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ANTITUMOR AND ANTIVIRAL AGENTS

Mechanisms of Action

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

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EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. EFFECT OF CIS-DICHLORODIAMMINEPLATINUM(II) ON CLONED OVARIAN ADENOCARCINOMA CELLS OF THE RAT IN VITRO.

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Gynecol Oncol; 12(1):14-22 1981

Cloned rat ovarian adenocarcinoma cells (ROT58/C3) treated for 1 hr with 0.5 ug/ml or more of cis-dichlorodiammineplatinum(II) (DDP) or adriamycin (ADM) revealed a marked decrease in survival as estimated by the colony-forming method. Compared to cloned rat uterine adenocarcinoma cells (HTP/C1), the ROT58/C3 cells were more sensitive to the cytotoxic effect of both drugs. The survival of exponentially growing ROT58/C3 cells was reduced to less than 10% by a 0.5 ug/ml dose of DDP, as compared to a 1 ug/ml dose of ADM. Extensive morphological changes such as enlargement of the nuclear and nucleolar diameters, increase in the number of nucleoli, and the appearance of coarse and opaque chromatins were observed by optical and electron microscopy at as early as 48 hr after exposure to DDP for 1 hr. In addition, accumulation of cells at the G2 phase in the cell cycle was observed by flow microfluorometry. (Author abstract) (13 Refs)

2. IRREVERSIBLE BINDING OF REDUCTIVELY ACTIVATED STREPTONIGRIN TO NUCLEIC ACIDS IN THE PRESENCE OF METALS.

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Chem Biol Interact; 36(2):179-188 1981

The binding of streptonigrin (SN) to nucleic acids was studied in the presence of reducing agents and metals. Incubation of chemically reduced SN with DNA in vitro resulted in irreversible binding and complexes containing 1 mole of SN per 250 nucleotides were obtained. The presence of Zn++ increased this binding considerably to give complexes containing 1 mole of SN per 80 nucleotides. On the other hand, Mg++ decreased this binding. More drug was bound to the denatured DNA than to the native DNA. Max binding was obtained when SN was reduced in the presence of DNA. Increased binding was also obtained when the fully reduced SN was incubated with DNA. Considerably more SN was bound to DNA when activated enzymatically than with NaBH4. Studies with synthetic polynucleotides in the presence of Zn++ suggested that while SN has a high affinity for guanine residues, cytosine and adenine residues also serve as excellent substrates. These studies indicate that the active intermediate that binds to nucleic acids is unstable and may be derived from the fully reduced drug. These in vitro studies further suggest that Zn++ plays an important role in the binding of SN to DNA and may have implications for the biological actions of SN if similar reactions occurred in vivo. (Author abstract) (31 Refs)

3. EFFECTS OF ANTICANCER PLATINUM COMPOUNDS ON ESCHERICHIA COLI STRAINS WITH NORMAL AND DEFECTIVE DNA REPAIR CAPACITY.

Konishi H, Usui T, Sawada H, Uchino H, Kidani Y

Div. Internal Medicine, Faculty of Medicine, Kyoto Univ., 53 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606, Japan

Gan; 72(4):627-630 1981

The effects of anticancer platinum compounds on isogenetic strains of Escherichia coli with normal or defective DNA repair capacity were studied. Cis-dichlorodiammineplatinum (II) causes DNA damage that is repairable by the repair systems of bacteria, and the DNA lesion becomes mutational when processed by the excision repair system. Dinitrato (1R,2S-cyclohexanediamine)platinum (II) exhibits similar killing activity on E coli strains with both normal and defective DNA repair capacity. Thus, this compound may cause DNA damage that cannot be repaired by bacteria, or its killing activity may be due to effects other than DNA damage. (Author abstract) (12 Refs)

4. INHIBITION OF DNA POLYMERASE ALPHA BY BLEOMYCIN.

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Div. Medicine, Sidney Farber Cancer Inst., Harvard Medical Sch., Dept. Dermatology, Boston, MA, 02115

Biochem Biophys Res Commun; 101(3):734-739 1981

The actions of bleomycin (BLM) on synthetic single (poly[dA]-oligo-[dT]) and double (poly[dA-dT]) stranded templates and on DNA polymerase alpha were examined. The reducing agent DTE enhanced the inhibitory activity of BLM. Only in its presence did BLM have a limited effect on the replication of the single stranded template, assessed via DNA polymerase activity. A plateau of approx 35% inhibition occurred between 10 and 10,000 uM BLM. BLM inhibited double strand replication with or without DTE. In order to determine the site of action of BLM, preincubation of the enzyme or template was followed by physically removing the drug by dialysis. DNA polymerase and single and double stranded templates were separately preincubated in the presence of 2 milliM DTE with or without 0.1 milliM BLM. BLM irreversibly damaged the double stranded template (88% inhibition of replication). BLM had no effect on the single stranded template. Following removal of BLM from DNA polymerase, a 34% loss of enzyme activity was observed. It was suggested that the 35% inhibition of single stranded replication in the BLM dose response test resulted not from an effect on the homopolymer template but from an alteration of the DNA polymerase enzyme. A Hill plot indicated inhibition of the enzyme alone. BLM was found to have a limited irreversible effect on DNA polymerase alpha attributable to residual activity of the enzyme-inhibitor complex. (14 Refs)

5. SISTER-CHROMATID EXCHANGE INDUCTION IN CHINESE HAMSTER OVARY CELLS BY 8-METHOXYPSORALEN AND BRIEF PULSES OF LASER LIGHT. ASSESSMENT OF THE RELATIVE IMPORTANCE OF 8-METHOXYPSORALEN-DNA MONOADDUCTS AND CROSSLINKS.

Sahar E, Kittrel C, Fulghum S, Feld M, Latt SA

Genetics Div., Children's Hosp., Boston, MA

Mutat Res; 83(1):91-105 1981

The reaction between 8-methoxypsoralen (8-MP) and the DNA of Chinese hamster ovary cells (CHO) was promoted in a controlled manner by brief (no more than 20 nanosec), 5-14 milliJoule (mJ) pulses of near-UV laser light. A single laser pulse was sufficient to cause a significant elevation in the frequency of sister-chromatid exchanges (SCE) in CHO exposed to 0.75-1.2 x 10(-5) M 8-MP. Additional pulses, up to a total of four, stimulated more SCE production, but the increment decreased with each successive pulse. Very little additional SCE induction was observed beyond four pulses. As 8-MP concentration increased, so did the SCE frequency for a given number of laser pulses. Laser pulses of 15 mJ were more effective in inducing SCE than were 5 mJ pulses. The formation of 3H-8-MP-DNA adducts was an approx linear function of the number of laser pulses. The number of DNA crosslinks produced by 3H-8-MP increased more than linearly with the number of laser pulses. These results provide strong evidence that DNA crosslinks are not necessary for SCE induction, even with a potentially bifunctional agent. (48 Refs)

6. GENE AMPLIFICATION IN MOUSE TUMOR CELL LINES.

Martinsson T, Lundh L, Tenning P, Levan G
Dept. Genetics, Univ. Gothenburg, Gothenburg, Sweden
Cell Biol Int Rep; 5(8):772 1981

Several lines from the mouse ascites tumor SEWA were tested for methotrexate (MTX) resistance (r) and associated changes in chromosomal features. The SEWA tumor lines were highly MTX sensitive, but on prolonged exposure to increasing MTX doses, one of the lines developed MTXr at 10 ug/ml. Development of MTXr was associated with the appearance of double minute chromosomes (DM). Found even in cells resistant to 0.1 ug/ml, the DM were large and uniform in size, with av 6.6 DM/cell. Gradual increase to 10 ug/ml MTX increased the av number to 36.9 DM/cell. At the higher concentrations DM size varied, with many cells displaying much smaller DM. Homogeneously staining regions (HSR) originally present in this line persisted unchanged. The development of MTXr was accompanied by greatly increased production of a 20,000 mol wt intracellular protein whose wt correlates with that of mouse dihydrofolate reductase, the target enzyme for MTX. (4 Refs)

7. FAILURE TO INDUCE SISTER CHROMATID EXCHANGES (SCE) WITH METRONIDAZOLE.

Mahood JS, Willson RL
Biochemistry Dept., Brunel Univ., Uxbridge, Middlesex, England
Toxicol Lett; 8(6):359-361 1981

When cultured CHO-K1 and BHK-21 cells were treated with metronidazole for 24 hr and then examined by colchicine block for mitotic figures showing sister chromatid exchanges, no significant differences (p greater than 0.05) were seen between drug-treated and control cultures in an analysis of variance. These results agree with other published reports that metronidazole does not induce micronuclei in vivo in Trichomonas vaginalis, the induction of dominant lethal genes, or unscheduled DNA synthesis in cultured human fibroblasts. (18 Refs)

8. APHIDICOLIN: AN INHIBITOR OF DNA REPAIR IN HUMAN FIBROBLASTS.

Waters R
Dept. Genetics, Univ. Coll., Singleton Park, Swansea SA2 8PP, Wales
Carcinogenesis; 2(8):795-797 1981

Normal human fibroblasts and excision-deficient xeroderma pigmentosum (XP) fibroblasts were labeled in vitro with [3H]thymidine. They were then left unirradiated or exposed to 254 nanom UV. Cultures were then reincubated with media containing aphidicolin (2.5 ug/ml), an inhibitor of DNA polymerase alpha; with cytosine arabinoside (araC: 10(-4) M), an inhibitor of semi-conservative and repair replication; with both aphidicolin and araC; or neither compound. Analysis of DNA showed that UV-induced DNA single-strand breaks accumulated equally in normal fibroblasts exposed to araC or to aphidicolin. The presence of both compounds in the medium did not alter the results obtained with only one. Neither compound had any effect on the excision-deficient XP cells. The results indicate that DNA polymerase alpha does play a role in the excision repair of DNA. (14 Refs)

9. DNA SUPERCOILING, SHORTENING, AND INDUCTION OF SINGLE-STRAND REGIONS BY CIS-DIAMMINEDICHLOROPLATINUM(II).

Mong S, Daskal Y, Prestayko AW, Crooke ST
Bristol-Baylor Lab., Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Res; 41(10):4020-4026 1981

The compound cis-diamminedichloroplatinum(II) (CDDP) was found to bind to covalently closed circular supercoiled, covalently closed circular nonsupercoiled, and single-strand broken relaxed PM2 DNA and induce different types of DNA conformational changes. Using Kleinschmidt's technique, it was found that binding of CDDP decreased the DNA length to 75% of the original single-strand broken relaxed DNA without inducing superhelical conformational changes. CDDP also shortened the length of covalently closed circular nonsupercoiled DNA before a supercoiled conformation was generated. Single strand-specific nucleases were used to detect drug-induced DNA structural alterations. Local single-strand regions or regions of denaturation were detected by S1 nuclease from Aspergillus oryzae and by BAL-31 nuclease from Alteromonas espejiana BAL-31. The single-strand regions or local denaturation regions do not seem to be related to or caused by DNA superhelical conformational changes since they were detected at drug concentrations at which no significant DNA superhelical turns were found. DNA shortening, superhelical conformational changes, and local denaturation regions can be explained by the previously proposed 'DNA intrastrand cross-linking' model. (Author abstract) (31 Refs)

10. THE NATURE OF UNBALANCED CELL GROWTH CAUSED BY CYTOTOXIC AGENTS.

Ross DW
Hematology Lab., Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Virchows Arch [Cell Pathol]; 37(2):225-235 1981

The vol of cells grown in tissue culture following exposure to a wide variety of cytotoxic drugs or x-rays increases at a rate of 1 to 10% of cell mass per hr. The same phenomenon is seen in animal neoplasias and human leukemias. This increase in cell vol is the result of unbalanced cell growth with a resulting disproportionate synthesis of proteins and possibly other macromolecules in the cytoplasm and nucleus. The dose response curve for a decrease in cell survival as measured by cloning efficiency in tissue culture is quantitatively correlated with the dose response curve for inducing an increase in cell vol. This quantitative relationship makes feasible the use of the phenomenon of unbalanced cell growth as a measure of cell death in screening for cytotoxic drugs or in monitoring response to therapy. An hypothesis to explain this increase in cell vol following chemotherapy is that cells are by the action of these drugs induced into an abortive or unbalanced pseudocycle which is characterized by synthesis of substantial amounts of protein without other preparative steps for cell division. (Author abstract) (50 Refs)

11. DNA STRAND BREAKS AND REPAIR SYNTHESIS IN YOSHIDA SARCOMA: CELLS WITH DIFFERENTIAL SENSITIVITIES TO BIFUNCTIONAL ALKYLATING AGENTS AND UV LIGHT.

Carr FJ, Fox BW
(c/o Fox) Paterson Lab., Christie Hosp., Manchester M20 9BX, England
Mutat Res; 83(2):233-249 1981

Analysis of the incidence of DNA strand breaks induced in Yoshida sarcoma cells sensitive (YS) to and resistant (YR) to methylene dimethanesulfonate (MDMS) by MDMS (a bifunctional alkylating agent), UV radiation, and methyl methanesulfonate (MMS; a monofunctional alkylating agent) was carried out using an alkaline DNA unwinding-hydroxylapatite technique to detect the breaks. Treatment with up to 200 ug/ml MDMS in either exponential or plateau phase of growth produced almost identical numbers of breaks in both YS and YR cells in both growth phases when breaks were measured immediately after MDMS treatment; but when the cells were postincubated for up to 12 hr after MDMS treatment, the incidence of breaks was lower in YR than in YS cells throughout the period and for both growth phases. Treatment of these cells (prior to, during, or after MDMS treatment) with either 1-beta-D-arabinofuranosylcytosine or hydroyxurea, which inhibited gap closure, revealed equal incidence of breaks in YS and YR cells. When plateau-phase YS and YR cells were treated with UV light (5 or 20 joules/square meter), the incidence of strand breaks was similar in both lines up to 2 hr after treatment, when the incidence in YR cells declined to below that in YS cells. Treatment of YS and YR cells with MMS (50 mg/ml for 1 hr) produced no significant difference in the incidence of strand breaks at any time up to 12 hr after treatment; the decay in the number of breaks was much slower than that observed after MDMS treatment. When the rate of repair synthesis induced by MDMS amd MMS in YS and YR cells was assayed by the BND-cellulose method, YR cells showed greater repair activity in the 12-hr period after drug treatment, which agrees with the other results obtained here. YR and YS cells appear to have equal capacities for making repair incisions in DNA, but YR cells can close the incision-repair gaps more efficiently than can YS cells. (35 Refs)

12. CLASSIFICATION OF CHEMICAL AGENTS AS TO THEIR ABILITY TO INDUCE LONG- OR SHORT-PATCH DNA REPAIR IN HUMAN CELLS.

Francis AA, Snyder RD, Dunn WC, Regan JD
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 83(2):159-169 1981

The excision repair response of normal human fibroblasts (NHF) and of xeroderma pigmentosum (XP) cells to 33 chemicals was compared with that to UV irradiation (which is known to induce 'long-patch' repair of about 90 nucleotides) and to gamma irradiation (which is known to induce 'short-patch' repair of. 3-4 nucleotides) by the 5-bromodeoxyuridine (BrdU) photolysis assay that quantitates unscheduled DNA synthesis. The following chemicals induced long-patch repair of 30-70 nucleotides in length and may be classified as UV-mimetic agents: N'-acetoxyacetylaminofluorene, ICR-170, 4-nitroquinoline-1-oxide, diarylcarbamate, 7-bromomethylbenzanthracene, dimethylbenzanthracene-5,6-epoxide, 7beta,8alpha-diol-9beta,10beta-epoxybenzo[a]pyrene, 7beta,8alpha-diol-9alpha,10alpha-epoxybenzo[a]pyrene, ethyl methanesulfonate, methyl methanesulfonate, and N-hydroxy-1-naphthylamine. The other chemicals elicited short-patch repair in NHF cells; the measurable DNA repair activity was at the limit of resolution of the sucrose density gradient technique employed to assay it. XP cells could not repair damage by these latter chemicals to the same extent that NHF cells could. It appears that, for the chemicals tested here, the ability of an agent to elicit a long-patch DNA repair response from NHF is a property of the most active direct-acting carcinogens. (23 Refs)

13. EFFECT OF MITOMYCIN-C AND ADRIAMYCIN ON CULTURED HUMAN HEPATOMA CELL CYCLE PROGRESSION.

Sano H, Sasaki F, Une Y, Hata Y, Nakanishi Y, Uchino J, Kasai Y
First Dept. Surgery, Hokkaido Univ. Sch. Medicine, Sapporo, Japan
Gan No Rinsho; 27(10):1200-1204,A-57 1981

Eighth generation C-HC-20 cultured human hepatoma cells with a population doubling time of 30.4 hr were separated into individual culture bottles containing 2 x 10(4) cells/2 cc and were treated with mitomycin C (MMC) and/or adriamycin (ADR). Histograms of the cultured cells were made hr 48 and 72 after treatment. On the basis of a standard human dosage of the MMC (4 mg) or the ADR (10 mg), the cells were treated with MMC (20, 2, 0.2, or 0.02 ug/ml) and/or ADR (50, 5, 0.5, or 0.05 ug/ml). Hr 48 after a 1-hr exposure to the MMC, a marked increase in G2-M phase cells were observed with low concentrations of the MMC. Continuous or 1-hr exposure of the cells to the ADR resulted in an increase in G2-M phase cells for up to hr 72 after treatment. On the basis of the results, it was hypothesized that administration of ADR during the 48 hr period after 1-hr administration of low-dose MMC would result in enhanced effects. (17 Refs) (In JPN)

14. EFFECT OF ANTINEOPLASTIC AGENTS ON THE PROLIFERATIVE ACTIVITY OF HUMAN BREAST CANCER CELLS CULTURED IN VIVO IN THE DIFFUSION CHAMBERS.

Shamaev VI, Krutova TV, D'iachkovskaia RF, Korman DB
Section Kinetics of Chemical and Biological Processes, Inst. Chemical Physics, Moscow, USSR
Biull Eksp Biol Med; 91(7):77-79 1981

To evaluate the effect of thiophosphamide, methylnitrosourea, and diazane on proliferation of tumor cells, surgery specimens were placed in the diffusion chambers, which were implanted into the abdominal cavity of CBA mice. On day 3-7 after the implantation, animals received single ip injection of antineoplastic agent at the max tolerant doses. All three agents caused marked inhibition of mitotic index in cultured breast cancer cells. (11 Refs) (In RUS)

15. STUDY OF REPAIR OF DNA-PROTEIN CROSSLINKS INDUCED BY ANTINEOPLASTIC ALKYLATING AGENTS.

Lomova TIu, Shakhova IK, Shkodinskaia EN
Inst. Medical Genetics, Moscow, USSR
Biull Eksp Biol Med; 91(7):74-76 1981

The repair of DNA-protein crosslinks induced by antineoplastic alkylating agents embichin (EMC), sarcolysine (SL), and chlorophenacyl (CP) was studied in a culture of Chinese hamster fibroblasts. The differences in the yield of crosslinks and the rate of their repair were due to the structure of the organic group. (11 Refs) (In RUS)

16. EFFECT OF NITIDINE CHLORIDE ON THE LIFE CYCLE OF EHRLICH ASCITES CARCINOMA CELLS IN MICE.

Fan YJ, Zhou J, Li M

Inst. Medical, Pharmaceutical Sci. of Guangni Chuang Autonomous Region, Manning, People's Republic of China

Zhongguo Yaoli Xuebao; 2(1):46-49 1981

Nitidine chloride, an alkaloid isolated from Zanthoxylum nitidum (Roxb) has been shown to have antitumor activities against experimental tumors (eg leukemia L1210 and P388). Using autoradiography, its effect on the cell cycle of Ehrlich ascites carcinoma (EAC) was studied and results are described. The cell cycle time was found to be 38.8 hr. Times for the G1, S, G2 and M periods were 8.0, 25.8, 3.8 and 1.2 hr respectively, with a growth fraction of 0.86. When given ip to EAC-bearing mice, nitidine chloride decreased the mitotic index and increased the proportion of large-sized EAC cells, indicating a G2 block, but it had no effect on the tritium-TdR pulse labeling index. At 40 mg/kg, nitidine chloride appeared to have killing effects on S cells. It also exhibited significant inhibitory effects on DNA synthesis and lesser effects on RNA synthesis. (7 Refs) (In CHI)

17. QUANTITIVE ASPECTS OF THE FORMATION AND LOSS OF DNA INTERSTRAND CROSSLINKS IN CH INESE HAMSTER CELLS FOLLOWING TREATMENT WITH CIS-DIAMMINEDICHLOROPLATINUM(II) (CISPLATIN). II. COMPARISON OF RESULTS FROM ALKALINE ELUTION, DNA RENATURATION AND DNA SEDIMENTATION STUDIES.

Pera MF, Rawlings CJ, Shackleton J, Roberts JJ

Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Research Station, Nightingales Lane, Chalfont St. Giles, Buchinghamshire HP8 4SP, England

Biochim Biophys Acta; 655(2):152-166 1981

The formation of interstrand crosslinks in the DNA of cis-diamminedichloroplatinum(II) (cisplatin)-treated Chinese hamster cells has been demonstrated by three independent, highly sensitive techniques: namely those of alkaline elution, renaturation of crosslinked DNA and alkaline sucrose gradient velocity sedimentation. Simultaneous measurement of DNA break frequency by the first two methods and a computer model combined with the third enabled the calculation of crosslink frequency after application of low doses of cisplatin. Good agreement was found between the values obtained by the three methods used here, and also with those obtained by direct measurement of the amount of crosslinked hybrid DNA in density-labeled cells treated with higher doses of cisplatin. When measured by all three methods described here, crosslinking was found to increase during several hours after treatment and then to decrease with a half-life of between 12 and 24 hr. For low initial levels of crosslinking, this was largely attributed to an excision repair process, since the formation of breaks in DNA was only minimal. (Author abstract) (26 Refs)

18. QUANTITATIVE ASPECTS OF THE FORMATION AND LOSS OF DNA INTERSTRAND CROSSLINKS IN CHINESE HAMSTER CELLS FOLLOWING TREATMENT WITH CIS-DIAMMINEDICHLOROPLATINUM(II) (CISPLATIN). I. PROPORTION OF DNA-PLATINUM REACTIONS INVOLVED IN DNA CROSSLINKING.

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Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Buckinghamshire HP8 4SP, England

Biochim Biophys Acta; 655(2):146-151 1981

The presence of interstrand crosslinks in the DNA of cis-diamminedichloroplatinum(II) (cisplatin)-treated Chinese hamster cells was demonstrated by the formation of a species of hybrid-labeled DNA in cells that had been density and radioactivity prelabelled with a combination of [3H]thymidine and 2'-deoxy-5-bromouridine (BrdUrd) prior to treatment. The extent of crosslinking and of total binding of platinum to the DNA increased linearly with dose over a wide range of concentrations of cisplatin. Simultaneous measurement of the size of co-isolated 14C-labeled DNA from untreated cells permitted an estimate of the size of the crosslinked DNA and hence of the proportion of bound platinum involved in a crosslinking reaction. No increase in the proportion of crosslinking reactions occurred during several hours post treatment incubatio n of cells when crosslinks were measured by this technique, in contrast to other studies using different techniques to measure DNA interstrand crosslinking in cisplatin treated cells. The enforced high concentrations of cisplatin required by this method to detect crosslinks precludes studies of their possible repair. (Author abstract) (21 Refs)

19. ICRF 159-INDUCED CELL-CYCLE PERTURBATION IN VITRO: ITS RELATIONSHIP TO INHIBITION OF COLONY-FORMING ABILITY.

Edgar DH, Creighton AM

Dept. Immunology, ARC Inst. Animal Physiology, Babraham, Cambridge CB2 4AT, England

Br J Cancer; 44(2):236-240 1981

The effects of single doses of ICRF 159 (Razoxane) on the cell-cycle kinetics of lines of BHK 21S cells in vitro were studied by means of flow microfluorometry (FMF). A characteristic accumulation of cells in the 4n DNA region after 6 hr in the presence of ICRF 159 was evident in cells which were sensitive to the cytotoxic effects of the agent, as judged by colony-forming assays. The subsequent accumulation of 8n cells as the major population within 24 hr indicates that this 6 hr effect is associated with the induction of tetraploidy through abnormal mitosis, rather than reflecting a G2 block of potential value in combination therapy. In ICRF 159-resistant sublines, the cell-cycle distributions were similarly affected, but only by doses of the drug high enough to reduce their surviving fraction. Somatic cell hybrids from crosses between sensitive and resistant cells demonstrated intermediate responses to ICRF 159, both in terms of cell-cycle kinetics and impairment of reproductive integrity. These data suggest a relationship between the two manifestations of the cellular action of ICRF 159, and also a possible predictive role for FMF in the assessment of response to this particular agent. (Author abstract) (14 Refs)

20. CHROMATIN ANALYSIS IN HUMAN ENDOMETRIAL ADENOCARCINOMA BEFORE AND AFTER TREATMENT WITH 6-METHYL-17-HYDROXYPROGESTERONE ACETATE (MPA).

Barni S, Novelli G, Zanoio L, Gerzeli G, Vecchietti G
Istituto di Anatomia Comparata, Universita di Pavia, Piazza Botta 10, I-27100 Pavia, Italy
Virchows Arch [Cell Pathol]; 37(2):167-177 1981

Some molecular and ultrastructural characteristics of chromatin (propidium iodide intercalation into DNA during thermal denaturation. DNA content per nucleus and its hydrolysis kinetics, euheterochromatin ratio) were studied in the cells of endometrial adenocarcinomas following oral treatment with 6-methyl-17-hydroxyprogesterone acetate (MPA) at a dose of 1 g/day for 12 days. Ultrastructurally, before treatment the nuclei of tumor cells were often irregularly shaped and exhibited a mostly dispersed chromatin (euchromatin). In addition, the distribution of DNA content per cell was clearly abnormal, reaching ploidy levels of 16c. From a physicochemical standpoint, both the thermal denaturation and the HCl-hydrolysis of DNA revealed a high lability of chromatin. After progestin treatment, nuclear morphology appeared to approach normality, and large areas of heterochromatin reappeared which, after staining with propidium iodide, could be seen as strongly fluorescent points. DNA showed a higher resistance to thermal denaturation, especially evident at temperatures exceeding 70 C. Also the HCl-hydrolysis curves showed that, particularly with regard to short (less than 20 min) or protracted (greater than 140 min) hydrolysis times, DNA was less easily hydrolyzed than before MPA-treatment. A clearcut modification could be observed with regard to the DNA content per cell, high ploidy levels disappearing and values being less dispersed. On the whole, these findings demonstrated an effect of the drug on tumor cells, particularly affecting chromatin, at least with regard to the parameters examined. (Author abstract) (18 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

21. TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITIES AND GLUCOCORTICOID RECEPTORS IN LEUKAEMIA.

Sasaki R, Takaku F, Aoki T, Bollum FJ, Saito T, Dan S
Dept. Haematology, Jichi Medical Sch., 3311-1 Yakushiji Minamikawachi-Machi, Kawachigun, Tochigi 329-04, Japan
Br J Cancer; 44(1):63-67 1981

The relation between terminal deoxynucleotidyl transferase (TdT) activity, glucocorticoid (GC) receptors and the effect of vincristine-prednisolone (VP) therapy on fresh leukemia cases was examined. Five of six TdT+ leukemias showed high levels of GC receptors and a favorable response to VP therapy, whereas one acute lymphoblastic leukemia and three of chronic myelogenous leukemia cases in blast crisis with no TdT activity showed low level of GC receptors and poor response to VP therapy. Significant correlation (r = 0.821, p less than 0.01) was observed between TdT activity and the number of GC receptor sites in these cases. Chi square test showed significant difference (p less than 0.01) between TdT+ and TdT- leukemias in the effect of VP. A significant difference (p less than 0.01) was also observed between VP-effective and ineffective leukemias in the number of GC-receptor sites by unpaired t test. Therefore GC receptors may be responsible for the effect of VP on TdT+ leukemias. (Author abstract) (18 Refs)

22. GUANINE NUCLEOTIDE DEPLETION AND TOXICITY IN MOUSE T LYMPHOMA (S-49) CELLS.

Cohen MB, Maybaum J, Sadee W
(c/o Sadee) Dept. Pharmacy, Sch. Pharmacy, Univ. California, San Francisco, CA, 94143
J Biol Chem; 256(16):8713-8717 1981

Incubation of mouse T lymphoma (S-49) cells with the inosinate dehydrogenase inhibitor mycophenolic acid produced a depletion of both GTP and dGTP, and resulted in growth inhibition, partial reduction in RNA synthesis, and drastic inhibition of DNA synthesis. Similar results suggested to others that the depletion of dGTP is primarily responsible for toxicity. However, guanosine was as effective as deoxyguanosine at preventing mycophenolic acid toxicity although deoxyguanosine was more effective at elevating dGTP levels. Moreover, in hypoxanthine-guanine phosphoribosyl-transferase-deficient mutants of S-49 (6MPR-3-3) deoxyguanosine was unable to prevent mycophenolic acid toxicity or to re-establish normal DNA synthesis, although it returned cellular dGTP but not GTP levels to normal. No other nucleotide levels changed in a way which could account for the toxicity. Incubation of cells with a combination of deoxyadenosine, deoxycytidine, and erythro-9-(2-hydroxy-3-nonyl)adenine produced a selective depletion of dGTP to levels similar to that produced by mycophenolic acid, but did not affect cell growth. Studies with cells synchronized by centrifugal elutriation show that the toxicity of mycophenolic acid is specific to the S-phase of the cell cycle. Addition of actinomycin D at a concentration that inhibited RNA synthesis increased the availability of GTP and re-established normal DNA synthesis in mycophenolic acid-treated S-49 cells. These results suggest that the depletion of GTP rather than that of dGTP produces toxic effects in S-49 cells and that GTP is required for DNA synthesis. (Author abstract) (19 Refs)

23. MODE OF ACTION OF GCE: AN ACTIVE ANTICANCER PRINCIPLE ISOLATED FROM AN INDIGENOUS PLANT GYMNOSPORIA ROTHIANA LAWS.

Chapekar MS, Sahasrabudhe MB
Dept. Pathology, Arlington Hosp., George Mason Drive, Arlington, VA
Indian J Exp Biol; 19(4):333-336 1981

The mechanism of action of chloroform ether extract (GCE), obtained from the roots of the plant Gymnosporia rothiana Laws, on L-1210 and P-388 transplantable tumors from BDF1 mice was examined. The viability of P-388 cells following treatment with 1 and 10 ug GCE was reduced to 68% and 58%, respectively, after 6 hr of drug exposure. After 4 and 6 hr of exposure to 100 ug GCE, the viability of P-388 cells was reduced to 58% and 27%, respectively. The viability of L-1210 cells was reduced to 40% and 0% after 6 hr of exposure to doses of 50 and 100 ug of GCE, respectively. In vivo animal bioassay studies indicated that GCE killed 90% and 98% of the cells after 2 and 6 hr in vitro exposures, respectively, of 1 x 10(6) cells to 100 ug GCE. For 10 ug of GCE, inhibition of DNA, RNA, and protein biosynthesis was 17%, 19%, and 50%, respectively. At 80 ug GCE, inhibition of the macromolecules was about 70%. Administration of 25 ug/kg GCE/mouse to L-1210 tumor bearing mice led to max protein synthesis inhibition after 12 hr of GCE treatment, max RNA synthesis inhibition after 24 hr, and max DNA synthesis inhibition after 36 hr. (11 Refs)

24. ANTITUMOR EFFECT OF DICYCLOHEXYLAMMONIUM SULFATE, A POTENT INHIBITOR OF SPERMIDINE SYNTHASE.

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Gan; 72(4):512-516 1981

The antitumor effect of dicyclohexylammonium sulfate (DCHA), a potent inhibitor of spermidine synthase, was tested on mice inoculated with Ehrlich ascites carcinoma, Ehrlich solid carcinoma and solid sarcoma-180. DCHA prolonged the survival time of mice bearing Ehrlich ascites carcinoma at doses of 50-100 mg/kg/day x 5. For Ehrlich solid carcinoma and solid sarcoma-180 the tumor growth was suppressed significantly at doses of 2-50 mg/kg/day x 10. The spermidine concentration of the tumor cells was lowered, while the spermine concentration hardly changed. The depletion of spermidine in the tumor cells might be a cause of the suppression of tumor growth. (Author abstract) (24 Refs)

25. CONTRASTING EFFECTS OF MAYTANSINE AND VINBLASTINE ON THE ALKYLATION OF TUBULIN SULFHYDRYLS.

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Arch Biochem Biophys; 210(2):498-504 1981

The effects of maytansine (MAY) and vinblastine (VIN) on the accessibility of the sulfhydryl groups were compared. MAY and VIN both bind to tubulin, are competitive inhibitors of each other's binding, and strongly inhibit microtubule assembly in vitro, but MAY (unlike VIN) does not induce tubulin aggregation or stabilize colchicine binding. VIN (10 uM) inhibited the reaction of bovine brain tubulin with 14C-iodoacetamide by 45%; MAY (up to 100 uM) had no effect; but MAY was a potent inhibitor of VIN's effect. This competition is consistent with a model in which the two drugs compete for the same or overlapping sites but suggests that the nature of the binding of each drug is different. The suppression of alkylation of tubulin induced by colchicine or podophyllotoxin was not affected by MAY, suggesting that MAY and VIN bind to different sites. Both MAY and VIN were able to increase the formation of beta-ef (an electrophoretically faster migrating form of beta-tubulin that apparently contains an intrachain crosslink) by the bifunctional reagent N,N'-ethylenebis-(iodoacetamide), showing that, at least in the portion of the tubulin molecule involved in beta-ef formation, VIN and MAY have similar effects. Since MAY does not seem to suppress competing alkylation reactions, the enhancement of beta-ef formation may represent a genuine conformational effect. Since the sulfhydryl groups of tubulin may be involved in regulating microtubule assembly, MAY and VIN may differ in the manner in which they inhibit microtubule assembly. (18 Refs)

26. THE EFFECT OF IN VIVO DOXORUBICIN (ADRIAMYCIN) AND ACLACINOMYCIN ADMINISTRATION ON GUANYLATE CYCLASE ACTIVITY IN RAT TISSUES.

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Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15261

Proc Soc Exp Biol Med; 167(4):459-462 1981

The effects of doxorubicin (DOX), aclacinomycin (ACM) 4-epi-doxorubicin (E-DOX), 7-OMEN, and quelamycin (QUE) on guanylate cyclase (GC) activity in rat tissues after in vivo administration were investigated. Male Sprague-Dawley rats were injected ip with a single dose of dimethyl sulfoxide (DMSO) or one of the drugs dissolved in DMSO. With 20 mg/kg DOX, GC activity was unchanged at 4 hr, but activity in the heart was significantly depressed after 24 hr and remained so for at least 72 hr. The inhibition of GC activity in kidney, liver, as well as heart was dose dependent, in contrast to results in an in vitro study which showed significant inhibition only in homogenates from heart tissue. With ACM, GC activities remained unchanged, when compared to controls, at all times and doses tested both in heart and liver. E-DOX inhibited GC in heart, while 7-OMEN and QUE (each at 20 mg/kg) had no effect. The mechanism of the inhibition of GC by DOX and its relationship to cardiotoxicity remains unknown. (8 Refs)

27. MALEIC VINYL ETHER ACTIVATION OF MURINE MACROPHAGES AGAINST LUNG-METASTASIZING TUMORS.

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Cancer Res; 41(10):3901-3906 1981

A.M.W. 15,500 fraction of maleic vinyl ether (MVE-2) induced tumoristatic and tumoricidal activity in peritoneal macrophages of BALB/c and C57BL/6 mice following ip administration. Growth of B16 melanoma cells in vitro was inhibited up to 85% by MVE-2-activated, but not resident, peritoneal macrophages. In a tritiated thymidine release assay, B16 melanoma cells, and to a lesser extent Madison 109 lung carcinoma cells, were also sensitive to the cytolytic action of MVE-2-activated peritoneal macrophages. Administration iv of MVE-2 resulted in tumoristatic and tumoricidal activity in alveolar macrophages against radiolabeled B16 and Madison 109 lung carcinoma target cells. MVE-2-activated alveolar macrophages significantly inhibited L5178Y lymphoma colony formation following a 48-hr macrophage-tumor coincubation. BALB/c mice bearing the lung-metastasizing Madison 109 lung carcinoma footpad tumor were given MVE-2 iv, using the same dosing regimen that induced alveolar macrophages to be tumoricidal in vitro. Significant increase in life span was observed, suggesting that the antitumor activity of MVE-2 in this tumor system may be mediated by the activation of alveolar macrophages, with a resulting decrease in metastatic growth in the lung. (Author abstract) (30 Refs)

28. DRUG SENSITIVITY AND SOME CHARACTERISTICS OF A BLEOMYCIN-RESISTANT SUBLINE OF MOUSE LYMPHOBLASTOMA L5178Y CELLS.

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Inst. Applied Microbiology, Univ. Tokyo, Tokyo, Japan
J Antibiot (Tokyo); 34(9):1210-1212 1981

A bleomycin (BL)-resistant subline of mouse lymphoblastoma L5178Y cells was isolated by the repeated injection of bleomycin A2 (BL-A: 10 mg/kg) in tumor-bearing CDFl female mice. The resistant cells grew more slowly than the parental cells; and the 50% inhibitory concentration (IC50) of BL-A on culture day 3 was 3.2 ug/ml for the resistant cells, vs 0.28 ug/ml for the parental cells. The IC50 for DNA-binding antibiotics (eg, adriamycin, neocarzinostatin, macromomycin, mitomycin C, aclacinomycin A) were similar for the resistant and parental cells; thus, these drugs showed no cross resistance with BL in the resistant cells. In contrast, cross resistance was observed with peplomycin. Measurements of BL-inactivating enzyme levels in the parental and subline cells showed that the resistance was not due to increased enzyme activity. The possibility that the resistance is due to plasma membrane alterations is discussed. (6 Refs)

29. THE ACTIONS OF VARIOUS CYTOCHALASINS ON MOUSE ADRENAL TUMOR CELLS IN RELATION TO TROPHIC STIMULATION OF STEROIDOGENESIS.

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Biochim Biophys Acta; 676(3):338-344 1981

Inhibition of the steroidogenic responses to ACTH and dibutyl cyclic AMP in Y-1 cells by four cytochalasins (E, D, B and H2B) was examined to determine whether the capacities of these agents to inhibit these responses could be related to their abilities to inhibit polymerization of actin from Y-1 cells and to their relative potencies in causing rounding of the same cells. Two steroidogenic responses were examined: production of 20alpha-dihydroprogesterone and transport of cholesterol to inner mitochondrial membrane. The relative potencies of the four cytochalasins were compared on the basis of the concentrations (ED50) required to produce half-max rate of rounding and those required to produce 50% inhibition of the steroidogenic responses to ACTH and dibutyl cyclic AMP and 50% inhibition of initial velocity of polymerization of Y-1 cell actin in 1 mM magnesium. The four cytochalasins were ranked in the same order of decreasing potency in all of these determinations (E greater than D greater than B greater than H2B). Moreover, each cytochalasin showed approx the same ED50 for all of the determinations. From these findings approx the same potency ratios were observed for the different cytochalasins in these parameters, namely E greater than D x 10; D greater than B x 9.3 and B greater than H2B x 1.3. These findings suggest that the cytochalasins inhibit steroidogenesis and produce rounding of cells by interfering with polymerization of actin and not as the result of effects unrelated to binding to actin. Similar results were obtained in serum-free medium. These obse rvations lend further support to the hypothesis that the steroidogenic responses to ACTH and dibutyl cyclic AMP require microfilaments which are involved in the intracellular transport of cholesterol. (Author abstract) (28 Refs)

30. BASIC AND APPLIED RESEARCH IN THE STUDY OF INDAZOLE CARBOXYLIC ACIDS.

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Chemotherapy; 27(Suppl2):9-20 1981

Numerous 1-substituted derivatives of indazole-3-carboxylic acids were tested for pharmacologic activity. Several showed antispermatogenic activity, embryotoxicity, and antitumor activity in Lewis lung tumor and sarcoma 180. It is hypothesized that the target for the activity of these compounds is the condensed mitochondrion or its functional equivalent, since these three systems have high energy requirements that are satisfied at low relatively oxygen tension. (9 Refs)

31. INHIBITION OF AMINOACYLATION OF TRANSFER RNA AND INDUCTION OF STRINGENT CONTROL IN ESCHERICHIA COLI BY 4-HYDROPEROXYCYCLOPHOSPHAMIDE.

Frank S, Eck W, Kersten W, Ogilvie A
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Hoppe Seylers Z Physiol Chem; 362(8):1059-1068 1981

The compound 4-Hydroxycyclophosphamide, a highly cytotoxic derivative of cyclophosphamide, has bacteriostatic properties at concentrations higher than 80 uM when given to Escherichia coli growing in glucose/salt medium. The inhibitory effect on growth, protein and RNA syntheses is relieved by the addition of a mixture of amino acids, with leucine being obligatory. In cells treated with the drug, aminoacylation of tRNALeu is drastically decreased, but the content of free leucine is not. It is concluded that 4-hydroxycyclophosphamide interferes with the charging process of tRNALeu in E coli leading to an inhibition of protein synthesis. The concomitant inhibition of RNA synthesis can adequately be explained by the stringent response phenomena. In a relaxed mutant strain of E coli, protein synthesis is also inhibited, but the accumulation of RNA continues after the addition of the drug. Guanosine tetraphosphate, the putative mediator of the stringent control, accumulates in drug-treated stringently controlled E coli but not in the relaxed mutant. An additional direct effect of the drug on RNA synthesis can therefore be ruled out. (Author abstract) (27 Refs)

32. IMMUNOSUPPRESSIVE EFFECT OF CYCLOPHOSPHAMIDE ACTIVATED IN VITRO BY LIVER MICROSOMES FROM MICE OF DIFFERENT STRAINS.

Telegin LIu, Zhirnov GF, Mazurov AV, Pnevnitskii LA
Lab. Immunogenetics, Inst. Medical Genetics, Moscow, USSR
Biull Eksp Biol Med; 91(7):57-60 1981

To test the hypothesis that the differences in the immunosuppressive activity of cyclophosphamide (CP) are due to the interstrain differences in the sensitivity, CP was incubated with liv er microsomes from CBA, BALB/c, and DBA/2 mice. The max rate of CP hydroxylation during incubation of liver microsomes from BALB/c mice was correlated with the highest content of cytochrome P-450. (18 Refs) (In RUS)

33. ALTERATION OF MEMBRANE-ASSOCIATED ENZYMES IN DRUG-RESISTANT SUBLINES OF MOUSE LYMPHOBLASTOMA L5178Y CELLS.

Sugimoto Y, Nishimura T, Suzuki H, Tanaka N
Inst. Applied Microbiology, Univ. Tokyo, Tokyo 113, Japan
J Antibiot (Tokyo); 34(9):1200-1205 1981

Activities of marker enzymes for various cell components were studied with extracts of adriamycin-, aclacinomycin A- and bleomycin-resistant cells and with partially purified plasma membrane fractions of aclacinomycin A-resistant cells, in comparison with those of the parental cells. Alkaline phosphodiesterase and Na+ K+ ATPase activities were observed to alter the drug-resistant sublines, but other enzymes showed similar activities in the resistant cells to those in the parental cells. Alkaline phosphodiesterase activities in all the resistant sublines were higher than those in the parental cells. Na+ K+ ATPase activities of anthracycline-resistant sublines were lower and that in bleomycin-resistant cell line was higher than that of the parental cells. The adriamycin-resistant cells exhibited the same level of alkaline phosphodiesterase activity with the aclacinomycin A-resistant cells: Vmax was the same with, and the affinity was twice stronger than the parental cells. The bleomycin-resistant cells showed ca 30% Vmax in comparison with the sensitive cells, and 17 fold higher affinity than the parental cells. The current results, concerning changes of membrane-associated enzymes in drug-resistant sublines of L5178Y cells, support the assumption that the resistance is due to alteration of plasma membrane transport systems. (Author abstract) (14 Refs)

34. VITAMIN K3 (MENADIONE) INHIBITS THE GROWTH OF MAMMALIAN TUMOR CELLS IN CULTURE.

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Life Sci; 29(13):1387-1392 1981

The effects of vitamin K on the morphology and the growth of mouse neuroblastoma (P2), mouse melanoma (B-16) and rat glioma (C-6) cells in culture were studied. Vitamin K3 inhibited the growth (due to cell death and partial or complete inhibition of cell division) of all three cell types without causing any morphological differentiation. Vitamin K3 was more effective than vitamin K1. Neuroblastoma cells were more sensitive to vitamin K3 than were melanoma or glioma cells. Glioma cells did not grow in hormone-supplemented serum-free medium; however, both neuroblastoma and melanoma cells grew to a level 70-80% of that found in serum-supplemented medium. Neuroblastoma cells and melanoma cells cultured in serum-free medium exhibited a 2-3 fold higher sensitivity to vitamin K3 than those cultured in serum-supplemented medium. This suggests that serum factors attenuate the growth inhibitory effect of vitamin K3 on tumor cells in culture, probably by reducing the availability of this vitamin to the cells. Neuroblastoma cells were more sensitive to vitamin K3 than were melanoma cells even when they were treated in serum-free medium. The fact that uM concentrations of vitamin K3 inhibit the growth of tumor cells in culture suggests that this vitamin may be a potentially useful anticancer agent. (Author abstract) (11 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

35. ENHANCED ANTI-CANCER EFFECT BY COMBINING CYTOTOXIC DRUGS WITH THE PROSTAGLANDIN SYNTHESIS INHIBITOR FLURBIPROFEN.

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Br J Pharmacol; 74(1):208p-209p 1981

Approx 10(6) NC carcinoma cells were injected sc into the left flank of 250 female WHT/Ht mice. Drug treatment by mouth commenced on day 13; primary tumors were excised the next day. Survival was similar in controls and chemotherapy (1.4 mg/kg melphalan, 2 mg/kg methotrexate) groups but longer in mice given 2.5 mg/kg flurbiprofen (F) bid and even long with F + chemotherapy: respectively, 45, 49, 53.5, and 71 days. Mice given F alone or with chemotherapy had a lower incidence of distant metastases than controls, since after 120 days 15 and 16 vs 4 disease-free animals remained. Local recurrence at the excision site was also reduced in the two groups receiving F. F combined with cytotoxic chemotherapy prolongs survival time of mice after excision of primary NC tumors and reduces recurrence at the excision site. (3 Refs)

36. COMPARISON OF HYPERBARIC OXYGEN AND MISONIDAZOLE IN FRACTIONATED IRRADIATION OF MURINE TUMORS.

Suit HD, Maimonis P, Michaels HB, Sedlacek R
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Radiat Res; 87(2):360-367 1981

The enhancement ratios for hyperbaric oxygen and for misonidazole were determined using two transplanted syngeneic tumors (spontaneous mammary carcinoma and squamous cell carcinoma) in C3Hf/Sed mice, and the acute response of C3H mouse skin as the endpoints. Animals were irradiated when tumors reached 6-8 mm in size or 18 days after plucking hair of the right-leg thigh of tumor-free mice. Calculation of the radiation dose (which produced a local control of 50% of tumors) showed essentially the same enhancement ratios (1.45-1.55) for hyperbaric oxygen and misonidazole (0.3 mg/kg, ip). The response of normal mouse skin to radiation given in five equal doses indicated slightly greater enhancement ratio for hyperbaric oxygen (1.94) than for misonidazole (1.54). (26 Refs)

37. COMBINED RADIATION-PROTECTIVE AND RADIATION-SENSITIZING AGENTS. II. RADIOSENSITIVITY OF HYPOXIC OR AEROBIC CHINESE HAMSTER FIBROBLASTS IN THE PRESENCE OF CYSTEAMINE AND MISONIDAZOLE: IMPLICATIONS FOR THE 'OXYGEN EFFECT' (WITH APPENDIX ON CALCULATION OF DOSE-MODIFYING FACTORS).

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Radiat Res; 87(2):265-283 1981

The radiation sensitivity of both hypoxic and aerobic cells exposed simultaneously to radiation-protector cysteamine (CS) and radiation-sensitizing agent misonidazole (MD) was studied in a culture of V79 Chinese hamster fibroblasts. MD at 2.5 milliM (mM) was found to sensitize hypoxic V79 cells to radiation by a factor of 2.1. Addition of CS to hypoxic cells containing MD provided protection against the radiosensitization by MD at concentrations as low as 0.1 mM. In aerobic cells, protection was achieved at CS concentration of greater than 1 mM of CS; at CS concentration of 30 mM, aerobic cells were as resistant as hypoxic cells without drug but still not as resistant as hypoxic cells with 30 mM of CS. These findings indicate that addition of CS cancels the benefit of MD and thus increases the differential response of hypoxic and aerobic cells. (48 Refs)

38. SYNERGISTIC EFFECT OF 5-FLUOROURACIL AND N-(PHOSPHONACETYL)-L-ASPARTATE ON CELL GROWTH AND RIBONUCLEIC ACID SYNTHESIS IN A HUMAN MAMMARY CARCINOMA.

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Biochem Pharmacol; 30(15):2045-2049 1981

The biological effects of N-(phosphonacetyl)-L-aspartate (PALA) and 5-fluorouracil (5-FU) were examined singly, and in combination, on the growth of a human mammary carcinoma (MDA) cell line in culture. All combinations of 5-FU (2.5 x 10(-7) to 1.5 x 10(-5) M) and PALA (6.0 x 10(-5) to 3.6 x 10(-3) M) resulted in synergistic inhibition of cell growth as revealed by a 50% isobologram. To examine the biochemical basis for the synergism, measurements of the incorporation of [3H]-5-FU into total non-poly(A)- and poly(A)-RNA, and of the simultaneous incorporation of [14C]deoxyguanosine and [3H]deoxyuridine into DNA, were determined. The combination of 3.7 x 10(-5) M PALA and 1 x 10(-6) M 5-FU produced 65-85% inhibition of cell growth after continuous treatment for 1-3 days. Treatment of the cells for 3 or 24 hr with the same drug regimen produced approx a 170% increase in the incorporation of 1 x 10(-6) M [3H]-5-FU into poly(A)RNA in comparison to [3H]-5-FU treatment alone; exposure for 24 hr to 3.7 x 10(-5) M PALA and 1 x 10(-6) M [3H]-5-FU resulted in a 285% increase in the incorporation of [3H]-5-FU into non-poly(A)RNA. The incorporation of either [14C]deoxyguanosine or [3H]deoxyuridine into DNA was not inhibited by this drug regimen; however, the incorporation of [3H]deoxyuridine into DNA was elevated significantly upon 12 or 24 hr of exposure to PALA alone. PALA and 5-FU treatment resulted in a 75% reduction in the concentration of UTP and no change in the concentration of 5-fluorouridine-5'-triphosphate (5-FUTP) versus 5-FU treatment alone. Thus, the proportion of 5-FUTP in the total 5-FUTP + UTP pool was enhanced more than three-fold by the combination regimen. These results indicate that the synergistic effect of the combination of PALA and 5-FU on the growth of MDA cells correlates with an increased proportion of 5-FUTP in the pyrimidine nucleotide pool and, consequently, with an enhanced incorporation of 5-FU into RNA, but not with inhibition of DNA synthesis. (Author abstract) (25 Refs)

39. A NEW APPROACH TO CANCER CHEMOTHERAPY: SELECTIVE ENHANCEMENT OF TUMOR BLOOD FLOW WITH ANGIOTENSIN II.

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JNCI; 67(3):663-669 1981

Elevation of the mean arterial blood pressure to approx 150 mm Hg by infusion of angiotensin II resulted in an approx 5.7-fold selective increase in blood flow in tumor tissue without increasing blood flow in normal tissue. This finding of no autoregulation of blood flow in tumor tissue was made in an experiment on inbred DONRYU rats with sc transplanted AH109A solid tumors (Yoshida ascites hepatoma). Changes in tissue blood flow were measured by a thermo-electrical method. In another experiment in which DONRYU rats with sc transplanted AH272 solid tumors were used, the chemotherapeutic effect of mitomycin C on main tumors and lymph node metastatic foci was markedly enhanced in rats with angiotensin-induced hypertension, as compared to its effect in rats without angiotensin-induced hypertension. Thus a new approach to cancer chemotherapy has been demonstrated in which the delivery to tumor tissue of systemically administered anticancer drugs can be selectively enhanced. (Author abstract) (30 Refs)

40. STIMULATION BY RETINOIC ACID OF PROSTAGLANDIN PRODUCTION AND ITS INHIBITION BY TUMOR PROMOTERS IN MOUSE MYELOID LEUKEMIA CELLS.

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Gan; 72(4):488-497 1981

Retinoic acid induced lysozyme activity in mouse myeloid leukemia M1 cells. It also stimulated the synthesis and release of prostaglandins such as prostaglandin F2alpha, E2, and D2 by the cells. The particulate fraction of retinoic acid-treated M1 cells converted arachidonate to prostaglandins, and this conversion was almost completely inhibited by indomethacin. Retinol, retinal and retinyl acetate, but not the pyridyl analog of retinoic acid, also induced lysozyme activity and stimulated synthesis and release of prostaglandins. Indomethacin inhibited the induction of lysozyme activity by retinoic acid. The induction of lysozyme activity and the stimulation of prostaglandin E2 production were dependent on the concentration of retinoic acid. Kinetic studies showed that stimulation of prostaglandin E2 production by retinoic acid was followed by induction of lysozyme activity. The tumor promoters 12-O-tetradecanoylphorbol-13-acetate (TPA) and phorbol 12,13-didecanoate inhibited the induction of lysozyme activity by retinoic acid, but 4alpha-phorbol didecanoate and phorbol did not. TPA and phorbol 12,13-didecanoate, but not 4alpha-phorbol didecanoate, also inhibited the stimulation of prostaglandin E2 production by retinoic acid. These results suggest that stimulation by retinoic acid of prostaglandin E2 production in M1 cells is a prerequisite for the induction of lysozyme activity. On the other hand, both retinoic acid and TPA inhibited the induction by dexamethasone of phagocytic activity, which is a typical functional marker of differentiation of M1 cells, without causing significant growth inhibition. Suboptimal concentrations of retinoic acid and TPA had synergistic inhibitory effects on the induction of phagocytic activity of M1 cells by dexamethasone. (Author abstract) (27 Refs)

41. TYPING OF IMMUNOMODULATORS IN TERMS OF THEIR EFFECTS ON THE ELECTROPHORETIC PATTERN OF SERUM PROTEINS AND ANTITUMOR COMBINATION THERAPY BASED ON THIS TYPING.

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Gan; 72(4):471-478 1981

Changes of serum proteins have recently received much attention in studies of immunomodulators. In this work, changes of serum proteins, especially LB, were studied by gel electrophoresis of sera after administration of 23 immunomodulators or antitumor agents. Fourteen of the 23 compounds increased the concentration of LB in the serum of normal ddY mice when injected once ip. Six compounds caused a very rapid (day 1) increase of LB, and 8 agents caused a slow increase (day 4-day 10). On the basis of the results, these compounds were classified into type I (causing a rapid increase in LB; eg, lipopolysaccharide, dextran sulfate and poly(I)-poly(C)), type II (causing a slow increase in LB; eg, lentinan, TAK and PS-K), and type 0 (causing no increase in LB; eg, levamisole and bestatin). The antitumor activities of these three types of compounds in combination with lipopolysaccharide (type I) or lentinan (type II) were studied in an Ehrlich carcinoma-ddY mouse system. The results suggested that different types of compounds frequently showed synergistic antitumor activities. Typing of immunomodulators and the antitumor activities of combinations of these compounds are discussed. (Author abstract) (13 Refs)

42. ENHANCED CYTOSTATIC EFFECTIVENESS OF ANILINE MUSTARD AGAINST 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY TUMORS DURING REGRESSION IN RESPONSE TO OVARIECTOMY.

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Cancer Treat Rep; 65(7/8):567-574 1981

Sprague-Dawley rats bearing 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumors were treated with either of two aromatic alkylating agents, aniline mustard or melphalan, alone or combined with ovariectomy. Both drugs were applied once a wk for 8 wk. Eighty-four percent of the tumors responded to ovariectomy, 38% regressing completely and 46% regressing partially. Aniline mustard, though virtually ineffective as a single agent, appeared synergistic with ovariectomy: a 100% regression rate (72% complete, 28% partial) was observed for this combination. Treatment with melphalan was as effective as ovariectomy, but the combination of melphalan with ovariectomy was no more effective than either treatment alone. The end product of aniline mustard metabolism, p-hydroxyaniline mustard O-glucuronide, may be more extensively activated by beta-glucuronidase in hormonally regressing than in growing or stationary tumors. Intratumoral levels of beta-glucuronidase occurring in DMBA-induced tumors 4 days after ovariectomy were found to be similar to those in the aniline mustard-sensitive mouse plasma cell tumor ADJ/PC6. It remains to be more extensively studied whether an effect of endocrine treatment on tumor beta-glucuronidase levels, and possibly on intracellular distribution of enzyme, could be used therapeutically. An effectively scheduled cytostatic treatment (with a drug conjugate such as that formed metabolically from aniline mustard) in conjunction with ovariectomy might be effective in the treatment of hormone-responsive breast cancer. (Author abstract) (29 Refs)

43. INCREASE IN CYTOTOXICITY OF CYTOSINE ARABINOSIDE AND INHIBITION OF DEGRADATION OF CYTOSINE ARABINOSIDE TRIPHOSPHATE (ARA-CTP) BY HYDROXYUREA IN HUMAN LYMPHOBLASTIC CELLS.

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Res. Inst. Tuberculosis and Cancer, Tohoku Univ., Sendai-shi, Miyagi Pref. 980, Japan
Gan To Kagaku Ryoho; 8(2):248-255 1981

The relationship between the metabolism of cytosine arabinoside (ara-C) and the sensitivity to the drug, and the effect of hydroxyurea (HU) on this relationship were examined in human lymphoblastic cell lines, MOLT-4F, Raji, and Daudi cells. Inhibition of DNA synthesis by ara-C was marked in MOLT-4F, Raji, and Daudi, in decreasing order, in accordance with the growth inhibition and intracellular accumulation of ara-C nucleotides during 4 hr incubation. The ara-C nucleotide level was maintained by both production and degradation, but it was found that HU could increase the nucleotide level by inhibiting the degradation in Raji and Daudi, whose dephosphorylating ability was high as compared to MOLT-4F. When ara-C incorporation was examined in the presence of 0.3 mM HU, the ara-C nucleotide level accumulated after 4 hr incubation was 3x higher than that in the absence of HU in Raji and Daudi. The nucleotide level was not changed by HU in MOLT-4F, which was poor in the dephosphorylation of the nucleotides. Since about 85% of the nucleotides were identified as ara-CTP by thin-layer chromatography, the change in ara-C nucleotides should reflect the change in ara-CTP. As a result of combination therapy carried out on the basis of the above observations, a marked synergistic effect was obtained in Raji, where the tumor cell reduction was seven-fold the expected value. The effect was additive in Daudi. The combination, however, gave no advantage to MOLT-4F, suggesting that the combination is preferable when the degradation of ara-CTP was concerned with the drug sensitivity. (Author abstract) (29 Refs) (In JPN)

44. RESPONSE OF L1210 LEUKEMIA TO TREATMENT WITH 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA PLUS 4'-DEMETHYLEPIPODOPHYLLOTOXIN-9-(4,6-O-2-THENYLIDENE BETA-D-GLUCOPYRANOSIDE).

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Cancer Res; 41(10):3891-3895 1981

Mice, inoculated ip with 1 million L1210 ascites cells, were treated subsequently with 1,3-bis(2-chloroethyl)-1-nitrosourea plus 4'-demethylepipodophyllotoxin-9-(4,6-O-2-thenylidene beta-D-glucopyranoside) in various combinations of dosages. The drugs were administered ip in rapid succession on one of four schedules. When treatment was administered on day 1, 24 hr after inoculation, all mice treated with 1 of 5 combinations of dosages survived for 60 days, apparently free of leukemia, and another 16 combinations of the drugs cured 50%, or more, of the animals. Treatment with combinations of lower dosages of the drugs on days 1, 4, and 7 was as effective as treatment with larger dosages on day 1; all mice treated with 5 combinations of the drugs survived, and 17 other combinations cured 50%, or more, of the mice. When mice were treated on similar schedules but the initiation of treatment was delayed until day 4, the therapeutic efficacy of the individual drugs and of the combinations decreased. Some of the mice survived for 60 days after treatment with both drugs on day 4, but the incidence was not greater than that achieved by treatment with the optimal dosage of 1,3-bis(2-chloroethyl)-1-nitrosourea on day 4. The schedule of treatment on days 4, 7, and 10 was the least effective, therapeutically, of the four schedules tested; only 12 of 235 mice survived for 60 days after treatment with the individual drugs or the drug combination. Because of a termination of the studies after 60 days, the data for all four studies were analyzed by the Cox multiple-regression technique. By this criterion, the incidence of mortality after treatment with the drugs on either day 1 or days 1, 4, and 7 was attributable in part to a therapeutic interaction between the drugs. This therapeutic interaction was not observed when mice were treated once on day 4. Analysis of the incidence of mortality after three courses of treatment, ie, treatment on days 4, 7, and 10, indicated that, although each drug was oncolytic, an interaction between the drugs reduced the effectiveness of the combination. 4'-demethylepipodophyllotoxin-9-(4,6-O-2-thenylidene beta-D-glucopyranoside) plus 1,3-bis(2-chloroethyl)-1-nitrosourea was remarkably effective for the treatment of L1210 leukemia, and on certain schedules the effectiveness resulted from a therapeutic interaction between the drugs. (Author abstract) (36 Refs)

45. PROTECTIVE ROLE OF THE GLUTATHIONE REDOX CYCLE AGAINST ADRIAMYCIN-MEDIATED TOXICITY IN ISOLATED HEPATOCYTES.

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Biochem Pharmacol; 30(16):2299-2304 1981

Incubation of isolated rat hepatocytes with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) resulted in the selective and extensive (greater than 90%) inactivation of glutathione reductase. BCNU also depleted intracellular glutathione by 70% but had no significant effect on cell viability or lipid peroxidation. Incubation of BCNU-treated hepatocytes with adriamycin (ADR) resulted in a decrease in cell viability concurrent with an increase in lipid peroxidation. These effects were not observed with untreated hepatocytes incubated with ADR. Glutathione depletion with diethylmaleate and incubation with ADR did not result in a significant decrease in cell viability or increase in lipid peroxidation. Incubation of BCNU-treated hepatocytes with ADR in the presence of exogenous alpha-tocopherol resulted in a significant amount of protection from ADR-mediated damage. (Author abstract) (47 Refs)

46. CORRELATION OF THYMIDINE-ENHANCED INCORPORATION OF ARA-C IN DEOXYRIBONUCLEIC ACID WITH INCREASED CELL LINE.

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Biochem Pharmacol; 30(16):2221-2224 1981

The treatment of L1210 cells with 10(-3) or 10(-4) M thymidine prior to cytosine arabinoside (ara-C) exposure increased significantly the incorporation of ara-C in DNA. Furthermore, the increased formation of (ara-C)DNA correlated with an enhanced loss of clonogenic survival (p less than 0.0001). Thymidine pretreatment at either concentration for 16 hr was more effective than a 2-hr pretreatment. The results suggest that the increased formation of (ara-C)DNA is, in part, related to the enhancement of cells traversing through S-phase following thymidine exposure. These results extend our previous observations showing a highly significant relationship between the extent of ara-C incorporation in DNA and loss of clonogenic survival. The incorporation of ara-C in DNA is a useful and easily measurable parameter for evaluating the effects of agents that modulate ara-C metabolism. (Author abstract) (8 Refs)

47. IN VIVO INHIBITION OF THE DEVELOPMENT OF MYELOID LEUKEMIA BY INJECTION OF MACROPHAGE- AND GRANULOCYTE-INDUCING PROTEIN.

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Int J Cancer; 28(3):375-386 1981

Injection of macrophage- and granulocyte-inducing protein (MGI) can inhibit the development of myeloid leukemia in vivo and stimulate normal myelopoiesis. The MGI injected contained MGI-I activity that induces colony formation with normal myeloblasts, and MGI-2 activity that induces differentiation of normal and MGI 7+ 1D 7+ 1 leukemic myeloblasts to mature macrophages or granulocytes. Injection of MGI reduced the tumor vol in mice sc inoculated with leukemic cells at least 50-fold The median survival time of MGI 7+ 1D 7+ 1 cells or sc with MGI 7+ 1D 7-1 cells was increased by about 40%, and 50% of the MGI-treated mice inoculated sc with MGI 7+ 1D 7+ 1 cells did not develop tumors. MGI also increased the anti-tumor effect of cyclophosphamide. The leukemia-inhibiting activity in the injected MGI preparations was associated with the peak of MGI activity separated on a hydroxylapatite column and was destroyed by treatment at the temperature which destroys MGI-2 activity. This indicates that the inhibition of leukemia development was mediated by MGI-2. It is suggested that improved schedules of MGI treatment, with or without compounds used in the cytotoxic types of therapy, should be able to give an even better inhibition of leukemia development and that these results should also be applicable to the therapy of human myeloid leukemia. (61 Refs)

48. EFFECT OF DE NOVO PURINE SYNTHESIS INHIBITORS ON 5-FLUOROURACIL METABOLISM AND CYTOTOXICITY.

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Biochem Pharmacol; 30(17):2469-2472 1981

Methotrexate pretreatment of L1210 cells had been shown previously by us to cause an enhancement of the intracellular accumulation of 5-fluorouracil and of the formation of 5-fluorouracil nucleotides which was correlated with synergistic cytotoxicity. This effect of methotrexate were associated with increases in 5-phosphoribosyl-1-pyrophosphate, the cofactor required for the conversion of 5- fluorouracil to 5-fluorouridine-5'-monophosphate. Because these influences on 5-fluorouracil metabolism were most likely mediated by the activity of methotrexate as an inhibitor of purine synthesis, the effects of other agents that inhibit purine synthesis were examined. An inhibitor of amidophosphoribosyltransferase, 6-methylmercaptopurine ribonucleoside, the glutamine antagonists, azaserine and 6-diazo-5-oxo-L-norleucine, and the L-aspartate analogue inhibitor of adenylsuccinate synthetase, L-alanosine, all reduced the incorporation of [1-14C]glycine into adenine and guanine bases isolated from nucleic acids. Each drug also resulted in intracellular elevations of 5-phosphoribosyl-1-pyrophosphate that were 15-to 25-fold greater than control levels. These alterations in de novo purine nucleotide synthesis were associated with enhanced intracellular 5-fluorouracil accumulation and synergistic cytotoxicity. (Author abstract) (26 Refs)

49. IMMUNOCHEMICAL STUDIES OF DNA MODIFIED BY CIS-DICHLORODIAMMINEPLATINUM(II) IN VIVO AND IN VITRO.

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Cancer Res; 41(10):4127-4131 1981

Two rabbits were immunized with native DNA modified in vitro by cis-dichlorodiammineplatinum(II) (cis-PT). The interactions between the antiserum and several natural and synthetic nucleic acids were studied primarily by radioimmunoassays. Native DNA's modified by platinum compounds with labile groups in the cis position are recognized by the antiserum. No cross-reaction is found with native DNA's substituted by other platinum compounds [trans-dichlorodiammineplatinum(II), cis-diamminotetrachloroplatinum(IV), and chlorodiethylenetriaminoplatinum(II)] and with natural and synthetic modified polyribonucleotides. cis-Pt-modified oligodeoxyribonucleotides and enzymatically hydrolyzed cis-Pt-modified native DNA do not bind to the antiserum. cis-Pt-modified double-stranded synthetic polydeoxyribonucleotides are either hardly recognized or not recognized at all. The antiserum recognizes a modified double-stranded helix in DNA which is not formed in several modified synthetic DNA's and RNA's. At least two different antigenic determinants are present in cis-Pt-modified DNA at a ratio of cis-Pt to bases equal to 0.05. Finally, the antiserum does not react with in vivo cis-Pt-modified DNA. (Author abstract) (28 Refs)

50. DEATH OF TUMOR CELLS IN RESPONSE TO THE USE OF A SYSTEM OF STIMULATED POLYAMINE UPTAKE FOR THE TRANSPORT OF METHYLGLYOXAL BIS(GUANYLHYDRAZONE).

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Eur J Biochem; 118(3):571-576 1981

Putrescine and spermidine depletion produced by alpha-difluoromethylornithine, a n irreversible inhibitor of ornithine decarboxylase (EC 4.1.1.17) greatly enhances the uptake of the anti-cancer drug methylglyoxal bis-(guanylhydrazone) by cultured Ehrlich ascites carcinoma cells. The drug was also more effectively retained in the cells previously exposed to the inhibitor of ornithine decarboxylase. When untreated Ehrlich ascites carcinoma cells were exposed to methylglyoxal bis(guanylhydrazone) and then transferred into drug-free medium, they rapidly reinitiated growth, while polyamine-deprived cells were irreversibly damaged upon similar exposure to the drug. Tumor cells with greatly reduced intracellular pools of putrescine and spermidine so effectively concentrated methylglyoxal bis(guanylhydrazone) that the drug largely disappeared from the medium resulting in a formation of concentration gradient of more than 5,000-fold across the cell membrane. The tumor cells tolerated high intracellular concentrations (6-9 mM) of methylglyoxal bis(guanylhydrazone) for less than 24 hr whereafter they disintegrated and excreted the drug back into the medium. The final destruction of the polyamine-depleted cells in response to methylglyoxal bis(guanylhydrazone) were preceded by profound inhibition of protein synthesis, which occurred before any disturbances in thymidine incorporation were obvious. The extent of polyamine depletion produced by difluoromethylornithine and the rate of the uptake of methylglyoxal bis(guanylhydrazone) were positively correlated to the growth rate of the tumor cells. Tumor cells with greatly reduced putrescine and spermidine pools concentrated methylglyoxal bis(guanylhydrazone) more rapidly than cells containing only moderately decreased concentrations of the polyamines. Although the uptake of exogenous spermidine by polyamine-deprived tumor cells was initially at least as rapid as that of methylglyoxal bis(guanylhydrazone), the transport of the natural polyamine was automatically halted when the intracellular spermidine pool was brought to a normal level. It thus appears that the uptake of methylglyoxal bis(guanylhydrazone) by the stimulated transport system of polyamines leads to a suicidal accumulation of the drug and to rapid cell death. (Author abstract) (18 Refs)

51. ANTI-TUMOUR ACTIVITY OF NOVEL ADDUCTS OF ASCORBIC ACID WITH ALDEHYDES.

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Eur J Cancer Clin Oncol; 17(7):759-765 1981

A novel adduct of ascorbic acid and methylglyoxal (MGA) inhibited the growth of the Ehrlich ascites carcinoma (EAC) in male CBA/Ca mice, following the ip injection of 5 x 10(6) tumor cells on day 0. MGA, 62.5 and 125 mg/kg-1 twice daily ip, inhibited tumor growth by 93% and 96%, respectively, when given on days 1-5 following transplantation. Treatment with MGA over days 5-9 after tumor cell injection was ineffective. A modified dose schedule, MGA 250 mg kg-1 ip, given as a single ip dose on days 1, 3 and 5 following transplantation, significantly increased the survival time of EAC-bearing mice. A number of related ascorbate (AsA) acetals were tested for antitumor activity using an identical experimental protocol. AsA-acetylacrolein was as active a growth inhibitor as MGA, inhibiting the growth of EAC by 97 and 98% (100 and 200 mg kg-1 twice daily, respectively). AsA-acrolein and AsA-glyoxal also inhibited the growth of EAC. Under identical conditions ascorbic acid, 200 mg kg-1 ip, twice daily, did not inhibit the growth of EAC, while the aldehydes methylglyoxal, 50 mg kg-1, and acetylacrolein, 12.5 mg kg-1, inhibited tumor growth by 98 and 99%, respectively. Combination of the aldehydes with ascorbic acid resulted in a considerable reduction in host toxicity; the LD50 for MG being 332 mg kg-1 and that for MGA 959-1,462 mg kg-1, for a single ip dose in mice. (Author abstract) (37 Refs)

52. EFFECT OF DIFFERENT PHYSIOLOGICAL CONDITIONS ON THE ACTION OF ADRIAMYCIN ON CHINESE HAMSTER CELLS IN VITRO.

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Abteilung fur Strahlenbiologie der GSF, Neuherberg, W. Germany
Br J Cancer; 44(2):241-246 1981

Chronically hypoxic cells were 5x more resistant to Adriamycin (ADR) than exponentially growing oxic cells. On reoxygenation, resistance decreased slowly to reach the ADR sensitivity of oxic cells after 24 h. With increasing pH, ADR efficiency increased more in oxic than in chronically hypoxic cells. With increasing cell density, ADR efficiency decreased linearly. The differences in ADR efficiency under the various conditions were accompanied by differences in intracellular ADR uptake. Chronically hypoxic cells incorporated 1.6x less than oxic cells; the incorporation rate at pH 6.5 was half that at pH 7.4; and at a cell density of 5 x 10(5)/bottle the intracellular uptake was 6x that at 5 x 10(6)/bottle. The observed differences in uptake of ADR were not, however, sufficient to explain the differences in cytotoxicity. (Author abstract) (11 Refs)

53. ENHANCED CYTOTOXICITY OF ANTINEOPLASTIC AGENTS FOLLOWING PROLONGED EXPOSURE TO MISONIDAZOLE.

Roizin-Towle LA, Hall EJ
Radiological Res. Lab., Dept. Radiology Cancer Center, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
Br J Cancer; 44(2):201-207 1981

Chinese hamster V79 cells cultured in vitro were used to investigate the cytotoxicity of various anti-cancer drugs subsequent to a prolonged treatment of the cells with misonidazole (MISO). The sensitivity of the cells to Bleomycin, Melphalan or Cisplatin was significantly increased by prior incubation with MISO under hypoxic conditions. When cysteamine, a radical scavenger, was present during the pretreatment with MISO, this enhancement of cytotoxicity was greatly reduced. These experiments, suggest that MISO by virtue of its selective toxicity towards hypoxic cells and its enhancement of cell killing by anti-neoplastic drugs, can play an important role in cancer chemotherapy. (Author abstract) (26 Refs)

54. MECHANISM OF ADRIAMYCIN CARDIOTOXICITY: EVIDENCE FOR OXIDATIVE STRESS.

Olson RD, Boerth RC, Gerber JG, Nies AS
Dept. Pediatrics, Vanderbilt Univ., Nashville, TN
Life Sci; 29(14):1393-1401 1981

Adriamycin is a widely used anticancer agent but the cumulative dose-dependent cardiotoxicity severely limits the use of adriamycin in the treatment of neoplastic diseases. Recent evidence suggests that adriamycin forms reactive free radical species which may oxidize cellular components and produce the cardiomyopathy. Sulfhydryl donors and antioxidants have been effective in preventing acute adriamycin cardiotoxicity in animal models presumably by scavenging the free radicals generated by adriamycin. The sulfhydryl donors, namely cysteamine and N-acetyl cysteine, do not interfere with adriamycin's antitumor activity. The results from these studies give considerable hope that the chronic cardiotoxicity from adriamycin may be attenuated in people, thereby giving additional therapeutic benefit from this antitumor agent. (Author abstract) (44 Refs)

55. EFFECTS OF MISONIDAZOLE ON TUMOR CELL RADIATION SENSITIVITY AND POTENTIALLY LETHAL DAMAGE REPAIR IN VIVO AND IN VITRO.

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Eur J Cancer Clin Oncol; 17(7):825-830 1981

The effects of misonidazole on the radiation response of a murine squamous cell carcinoma in vivo and on the radiation response of plateau phase cultures in vitro have been studied. From the analysis of the single cell survival curves for the in vivo tumors it has been concluded that misonidazole-induced effects are max during the first hr after injection, that a dose of 0.05 mg/g is marginally effective in reducing the survival following X-ray, but that a dose of 0.5 mg/g sensitizes both oxygenated (1.4-fold) and hypoxic (1.7-to 2.0-fold) tumor cells. In addition, it has been shown in vivo that a dose of 0.5 mg/g can inhibit the repair of potentially lethal damage. In vitro studies on plateau phase cultures of CHO cells have confirmed these in vivo observations, ie, 0.05 mg/ml of misonidazole sensitized plateau phase cultures in air by a factor of 1.2, and inhibited the repair of potentially lethal damage. These data would suggest that misonidazole is not simply cytotoxic for, or a radiosensitizer of, hypoxic cells. (Author abstract) (23 Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

56. INHIBITION OF TYROSINE AMINOTRANSFERASE INDUCTION BY UTP DEFICIENCY AND ITS REVERSAL BY 5-FLUOROURIDINE IN CULTURED HEPATOMA CELLS.

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Biochim Biophys Acta; 655(1):34-40 1981

Hepatoma tissue culture cells, grown in the presence of D-galactosamine and 6-azauridine, demonstrate a strong reduction of the intracellular UTP pool that can be replenished by formation of UTP from uridine and FUTP from 5-fluorouridine within 2 hr. Concomitantly with the UTP deficiency, a decrease of dexamethasone-induced tyrosine aminotransferase activity occurs. 5-Fluorouridine, as compared to uridine, is even more efficient in restoring the activity of tyrosine aminotransferase. Treatment of the cells with D-galactosamine alone results in a minor lowering of UTP that is not followed by the inhibition of the enzyme induction. However, the administration of D-galactosamine, simultaneously or at any time up to 5 hr before or after dexamethasone, leads to a 1.5-to two-fold higher induction (superinduction) which appears 24 hr later. (Author abstract) (39 Refs)

57. RELATIONSHIP OF THE RESISTANCE OF MAMMALIAN CELLS TO ACTINOMYCIN D WITH THE CHANGES OF THE KARYOTYPE AND DECREASED PERMEABILITY OF CELL MEMBRANE.

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Genetika; 17(7):1253-1258 1981

To evaluate the mechanism of resistance to antineoplastic agents, the homogeneously stained regions (HSR) were studied in chromosomes of cultured hamster cells resistant to actinomycin D (AD). Continuous culturing of AD-resistant cells in the absence of selecting agent resulted in gradual disappearance of resistance. Incubation of sensitive and resistant cells with 3H-actinomycin showed marked (approx 50-fold) decrease of label accumulation in resistant cells. These findings indicate that resistance to AD is associated with decreased permeability of cell membrane for AD. The presence of HSR in chromosomes of resistant cells could be interpreted as amplification of genes responsible for the synthesis of certain components of cell membrane. (17 Refs) (In RUS)

58. SPECIFIC RESISTANCE TO 8-AZAGUANINE IN CELLS WITH NORMAL HYPOXANTHINE PHOSPHORIBOSYLTRANSFERASE (HPRT) ACTIVITY: THE ROLE OF GUANINE DEAMINASE.

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Cytogenet Cell Genet; 30(2):118-128 1981

The role of guanine deaminase in selective cellular resistance to 8-azaguanine was examined, using eight mammalian cell lines and their subclonal derivatives isolated on the basis of increasing resistance to this drugs. 8-Azaguanine and 6-thioguanine are synthetic analogs of guanine and are lethal to cells with normal hypoxanthine phosphoribosyltransferase (HPRT) activity. In principle, however, HPRT-positive cells could become selectively resistant to 8-azaguanine if, by any mechanism, the cells expressed higher levels of guanine deaminase. This is because 8-azaguanine, but not 6-thioguanine, is converted by this enzyme to a noncytotoxic metabolite, 8-azaxanthine. Our study shows that HPRT-positive cells inherently resistant to relatively high levels of 8-azaguanine contain high levels of guanine deaminase. In general, guanine deaminase activity was higher in 8-azaguanine-resistant cells, regardless of their HPRT activity. Our results support the view that elevated guanine deaminase activity constitutes a potential mechanism of selective 8-azaguanine resistance in cells with normal HPRT activity. Guanine deaminase levels were significantly elevated in HPRT-positive cells briefly exposed to sublethal concentrations of 8-azaguanine, but this elevation was transient. Long-term exposure of cells to increasingly higher levels of the drug did not lead to high stable levels of guanine deaminase, indicating that 8-azaguanine is not an inducer of guanine deaminase in the cells examined. (Author abstract) (22 Refs)

59. INABILITY OF LIPOSOME ENCAPSULATED 1-BETA-D-ARABINOFURANOSYLCYTOSINE NUCLEOTIDES TO OVERCOME DRUG RESISTANCE IN L1210 CELLS.

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Eur J Cancer Clin Oncol; 17(7):809-817 1981

The uptake, metabolism and antitumor activity of 1-beta-D-arabinofuranosylcytosine nucleotides encapsulated in liposomes were investigated in L1210 cells sensitive and resistant to the drug. These studies were carried out in order to determine whether encapsulation of the presumed active component of the drug, namely, arabinofuranosylcytosine 5' triphosphate will convert resistant cells to sensitive. The results indicate that liposome entrapment of Ara-CMP and Ara-CTP did not result in increased delivery of these metabolites into L1210 cells. The amount of nucleotide found intracellularly following an in vitro incubation of encapsulated drugs with L1210 cells did not exceed the level expected from a simple extracellular breakdown of liposome releasing their contents with subsequent uptake and phosphorylation of the released nucleoside. Further evidence for lack of enhancement of drug uptake by liposome encapsulation was obtained when the rate of incorporation of TdR into DNA of L1210/Ara-C was not significantly affected by Ara-CTP encapsulation in liposome. The data presented herein also demonstrated that the in vivo sensitivity of L1210 cells resistant to Ara-C could not be modified by encapsulation of Ara-CTP in liposomes. The results strongly suggest that encapsulation of drugs unmodified or untargeted liposomes will not be able to ov ercome drug resistance related to transport defect and/or deletion of intracellular activating enzyme(s). (Author abstract) (23 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

60. MECHANISM OF THE EFFECT OF THE ANTICANCER ANTIBIOTIC NEOCARZINOSTATIN (NCS). VIII. SYNERGISTIC ACTION OF THE PROTEIN COMPONENT (PC) AND THE NONPROTEIN COMPONENT (NPC) (MEETING ABSTRACT).

Ebina T, Sato A, Edo K, Ishida N, Koide Y
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Nippon Saikingaku Zasshi; 36(1):232 1981

It was previously reported that neocarzinostatin (NCS) is composed of two components, PC and NPC, which differ from each other in the nature of their activity. In this study purified PC and NPC and a recombination of the two components were compared for their in vitro effects on paracrystal formation and spreading of cancer cells and on bacterial growth. Paracrystal formation by HeLa cells observed by phase-contrast microscopy and spreading of HeLa cells observed by Giemsa staining were not inhibited by single PC or NPC, and the marked inhibition of both phenomena shown by NCS was only partly restored by a mixture of PC and NPC at the same ratio as in NCS. The minimum inhibitory concentration for Sarcina lutea was 3.1 ug/ml for NCS and 12.5 ug/ml for NPC, whereas PC did not inhibit the bacterial growth even at 100 ug/ml. Since it was previously shown that in vitro cutting of DNA chains is caused by NPC, it is suggested that PC acts as a carrier of NPC for NPC to combine with the cell membrane. (no Refs) (In JPN)

61. N(2)- AND C-7-SUBSTITUTED ACTINOMYCIN D ANALOGUES: SYNTHESIS, DNA-BINDING AFFINITY, AND BIOCHEMICAL AND BIOLOGICAL PROPERTIES. STRUCTURE-ACTIVITY RELATIONSHIP.

Sengupta SK, Anderson JE, Kogan Y, Trites DH, Beltz WR, Madhavarao MS
Boston Univ. Medical Center, Sch. Medicine, Boston, MA, 02118
J Med Chem; 24(9):1052-1059 1981

N2-n-Alkyl- and omega-amino-n-alkylactinomycin D and 7-alkoxy-, 7-aralkoxy-, and 7-(acyloxy)actinomycin D were synthesized by modification of the parent actinomycin D molecule at the N2 and C-7 positions of the phenoxazinone moiety. The intermediate for N2 substitution was 2-deamino-2-chloroactinomycin D. For C-7 substitution, 7-hydroxyactinomycin D was used as the intermediate. Treatment of 2-deamino-2-chloroactinomycin D with an excess of the appropriate amine produced the N2-substituted derivatives. Condensation of the required alkyl or acyl halides with 7-hydroxyactinomycin D, aided by solid anhydrous potassium carbonate, yielded the C-7-substituted analogues. Calf thymus DNA-binding affinity was determined by equilibrium binding and also by thermal denaturation of DNA techniques, inhibitory activity of nucleic acid synthesis was examined using P388 cells in vitro, cytotoxicity measurements to tumor cells in vitro employed human lymphoblastic leukemic cells (CCRF-CEM), and antitumor activity was assayed against P388 mouse leukemia in CDF1 mice. Synthesis of a number of new analogues in each series and determination of the biophysical, biochemical, and biological properties established a more thorough structure-activity relationship in these analogues. These results establish that with the selection of omega-(n-alkylamino) groups at the N2 site or O-n-alkyl or O-acyl groups at the C-7 site a variety of modifications can be carried out on the actinomycin molecule while preserving biological activity. N2-3'-Amino-n-propyl- and N2-10'-amino-n-decylactinomycin D, 7-methoxy- and 7-ethoxyactinomycin D, and the 7-O-(1'-adamantoyl) ester of 7-hydroxyactinomycin D were found to be the most effective antitumor agents in vivo and in vitro. They also strongly inhibit cellular RNA and DNA synthesis and, with the exception of the ester, retain high DNA-binding affinity. (Author abstract) (41 Refs)

62. A POSSIBLE ROLE BY BITHIAZOLES OF BLEOMYCIN IN CAUSING DOUBLE-STRAND SCISSION OF DNA.

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J Antibiot (Tokyo); 34(9):1213-1215 1981

The role of the bithiazole group of bleomycin (BL) in the formation of DNA double-strand breaks (dsb) was evaluated by comparing the activity of BL and phleomycin (PH), which has a thiazoline group and is otherwise identical to BL. Covalently closed circular DNA (form I DNA) was used as the substrate, and the extent dsb and single-strand break (ssb) production was determined from the appearance of nicked, circular form II DNA and broken, linear form III DNA, respectively. The dsb:ssb values were larger for BL than for PH under conditions where the loss of form I DNA varied widely. This indicated that BL produced more dsb than did PH. The possible correlation between intercalation of the bithiazole group and dsb was evaluated by determining the effects of the intercalator ethidium bromide (EB) on the DNA-cleaving activity of BL and PH. High EB concentrations selectively inhibited the dsb activity of BL, with the result that the BL dsb:ssb values approaches those for PH. The result suggested that the BL bithiazoles are involved in dsb formation. (10 Refs)

63. SYNTHESIS OF 5,11-METHENYLTETRAHYDROHOMOFOLATE AND ITS ANTIFOLATE ACTIVITY IN VITRO.

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Dept. Chemistry, New York Univ., New York, NY, 10003

J Med Chem; 24(9):1086-1088 1981

The synthesis of 5,11-methenyltetrahydrohomofolate was accomplished by treatment of tetrahydrohomofolate (H4homofolate) with triethyl orthoformate in glacial acetic acid. This compound is a homofolate analogue of 5,10-methenyltetrahydrofolate which serves as one precursor to the 10-formyl one -carbon donor for the first transformylation in de novo purine biosynthesis, namely, the conversion of glycinamide ribonucleotide (GAR) to N-formylglycinamide ribonucleotide (FGAR), catalyzed by the enzyme glycinamide ribonucleotide transformylase (EC 2.1.2.2). The analogue proved to retard the rate of formation of formylglycinamide ribonucleotide apparently by inhibiting the rate of synthesis of 10-formyltetrahydrofolate, the actual cofactor for the transformylase enzyme, from 5,10-methenyltetrahydrofolate. Its inhibition of the enzyme, 5,10-methenyltetrahydrofolate cyclohydrolase (EC 3.5.4.9), was competitive against (+)-L-5,10-methenyltetrahydrofolate, with a Ki = 41 uM. This derivative of homofolate may be responsible for its inhibition of purine biosynthesis in Sarcoma 180 cells. (Author abstract) (23 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

64. A SIMPLE METHOD TO DETERMINE THE MODE OF ACTION OF DRUGS THAT INHIBIT DNA SYNTHESIS.

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Dept. Biochemistry and Molecular Biology, Inst. Basic Medical Sciences, Chinese Academy Medical Sciences, Beijing, People's Republic of China

Yaoxue Xuebao; 16(3):238-240 1981

Many drugs (especially anticancer drugs) exert their action by inhibiting the biosynthesis of DNA. This action can be classified into 2 types: (1) damage to the DNA template, which is usually irreversible; and (2) interference with DNA metabolism, which is usually reversible. Based on the incorporation of tritium-labeled thymidine by Ehrlich ascites carcinoma cells following drug treatment, the mode of action of anticancer drugs could be determined. Thus, decreased thymidine incorporation would suggest a mode of action through DNA template damage while increased thymidine incorporation would mean a mode of action through interference of DNA metabolism. Based on this principle, the anticancer drugs, nitrogen mustard, daunorubicin and zhingguangmycin (bleomycin A5) were found to exert their action on tumor DNA biosynthesis through damage of DNA templates. On the other hand, the inhibitory action of arabinoside cytosine, fluorouracil and methotrexate on DNA biosynthesis was through interference with DNA metabolism. These results agreed well with those determined by other methods. It is concluded that this method is simple and accurate in determining the mode of action of drugs that inhibit DNA biosynthesis. (8 Refs) (In CHI)

INTERFERON AND OTHER ANTIVIRALS

65. TOTAL SYNTHESIS OF A HUMAN LEUKOCYTE INTERFERON GENE.

Edge MD, Greene AR, Heathcliffe GR, Meacock PA, Schuch W, Scanlon DB, Atkinson TC, Newton CR, Markham AF

ICI Pharmaceuticals Div., Mereside, Alderly Park, Macclesfield, Cheshire SK10 4TG, England

Nature (Lond); 292(5825):756-762 1981

A 514-base pair fragment of double-stranded DNA coding for human interferon-alph a1 (166 amino acid residues), and containing initiation and termination signals plus appropriate restriction enzyme sites for plasmid insertion, has been totally synthesized. The synthesis involved preparation of 66 oligodeoxyribonucleotides, ranging in size from 14 to 21 residues, plus 1 deoxydecanucleotide, by rapid, solid phase procedures, and enzymatic ligation of the oligonucleotides. After ligation of the synthetic gene to a plasmid vector and transformation of Escherichia coli, clones containing the anticipated gene sequence were obtained. (Author abstract) (55 Refs)

66. INTERFERON PRODUCTION BY A HUMAN LYMPHOBLASTOID CELL LINE (DG-75) FREE OF THE EPSTEIN-BARR VIRUS GENOME.

Lazar A, Reuveny S, Minai M, Traub A, Mizrahi A
Biotechnology Dept., Israel Inst. for Biological Res., Ness Ziona 70450, Israel

Antimicrob Agents Chemother; 20(2):151-154 1981

A new lymphoblastoid cell line, DG-75, was investigated for its ability to produce interferon. DG-75 cells, previously shown to be free of Epstein-Barr virus genome and receptors, could be grown in submerged culture and could produce interferon in titers comparable to interferon produced by Namalva cells. The interferon produced was similar in size to the Namalva interferon as determined by gel filtration in Ultrogel AcA54. The DG-75 cells present a new source for large quantities of interferon which may be safer for human use than the Namalva interferon. (Author abstract) (21 Refs)

67. A MOUSE CELL LINE, WHICH IS UNPROTECTED BY INTERFERON AGAINST LYTIC VIRUS INFECTION, LACKS RIBONUCLEASE F ACTIVITY.

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Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, 9000 Rockville Pike, Bethesda, MD, 20205

Eur J Biochem; 118(1):9-15 1981

A mouse cell line, NIH 3T3, does not respond to some of the activities of interferon. Even after treatment with high concentrations of interferon the replication of lytic viruses, such as encephalomyocarditis virus (EMCV) and vesicular stomatitis virus (VSV) is not inhibited in these cells. In contrast, interferon treatment of these same cells results in the inhibition of Moloney murine leukemia virus (MMuLV) production. We have analyzed enzymatic pathways which are induced by interferon in these cells. After interferon treatment, the level of the (2'-5')oligoadenylate [(2'-5')An] synthetase activity and the phosphorylation of the 67,000-dalton protein (P1) are enhanced in NIH 3T3 cells to approx the same level as interferon-sensitive mouse L-cells. Moreover, NIH 3T3 and L-cells contain approx the same levels of enzymes which inactivate (2'-5')An. Both exogenously added (2'-5')A3 or double-stranded RNA (dsRNA) failed to inhibit protein synthesis in NIH 3T3 extracts even though they were potent inhibitors of L-cell extract-directed protein synthesis. Direct measurements of the (2'-5')An-dependent ribonuclease F (RNase F) failed to detect such activity in NIH 3T3 cells. Our results, therefore, suggest that the presence of RNase F activity is necessary for the interferon-induced antiviral activity against EMCV and against VSV. The induction of protein kinase activity by interferon treatment of NIH 3T3 cells appears to have no direct effect on EMCV and VSV replication. (Author abstract) (44 Refs)

68. INTERFERON ENHANCES THE AMOUNT OF MEMBRANE-BOUND BETA2-MICROGLOBULIN AND ITS RELEASE FROM HUMAN BURKITT CELLS.

Fellous M, Bono R, Hyafil F, Gresser I
Groupe de Recherches d'Immunogenetiques de la Transplantation Humaine, INSERM U 93, Hopital Saint-Louis, 2, Place du Dr. Fournier, F75475 Paris Cedex 10, France

Eur J Immunol; 11(6):524-526 1981

Human leukocyte interferon (HuIFN-alpha) increased the amount of beta2-microglobulin on the surface of human Burkitt lymphoma cells (Ramos) and also increased the amount released into the culture medium. The effect was observed 1 hr after addition of IFN. These results suggest that the increase in beta2-microglobulin on the cell surface of IFN-treated cells is not due to a decreased shedding of antigen from the cell surface, nor an 'unmasking' of surface antigen, but rather to an increased synthesis of antigen. (Author abstract) (38 Refs)

69. MECHANISM OF INTERFERON ACTION. INHIBITION OF PPPA(2'P5'A)N-DEPENDENT RIBONUCLEASE ACTIVITY IN MICROCOCCAL NUCLEASE-TREATED MOUSE L CELL-FREE EXTRACTS.

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Biochem Biophys Res Commun; 101(2):680-688 1981

The molecular basis by which the pppA(2'p5'A)n-dependent ribonuclease activity is blocked in micrococcal nuclease-treated as compared to nonpreincubated cell-free extracts prepared from interferon (IF)-treated mouse L cells was investigated. The micrococcal nuclease was purified from the Foggi strain of Staphylococcus aureus. Nonpreincubated and micrococcal nuclease-treated cell-free S-10 extracts were prepared from mouse L fibroblast cells grown in suspension culture. The mouse L cell-free extracts were supplemented with 2'-deoxythymidine-3',5'-diphosphate (pTp) and ethyleneglycol-bis(beta-aminoethyl ether)-N,N'-tetraacetic acid (EGTA) to catalyze the 2'-5'-oligo A tetramer enhanced degradation of reovirus [3H] messenger (m)RNA. Results indicated that (1) digestion of endogenous cellular RNA by the micrococcal nuclease during the preparation of the mRNA-dependent protein synthesizing system is required to establish the apparent inhibition of the 2',5'-oligo A-dependent ribonuclease, and (2) neither pTp nor EGTA directly affected the activity of either the 2',5'-oligo A synthetase or the 2',5'-oligo A-dependent ribonuclease in mous e L cells. (18 Refs)

70. LACTATE DEHYDROGENASE-ELEVATING AGENT IS RESPONSIBLE FOR INTERFERON INDUCTION AND ENHANCEMENT OF NATURAL KILLER CELL ACTIVITY BY INOCULATION OF EHRLICH ASCITES CARCINOMA CELLS INTO MICE.

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Microbiol Immunol; 25(6):565-574 1981

Ehrlich ascites cells (EAC; 10(6) cells) passaged in the peritoneum of outbred male ddY mice induced interferon (IFN) in the serum with a max of 1,280 antiviral units in the pooled serum/3 mice. A study of properties of the IFN indicated it had characteristics of IFN (stability at pH 2 and lability at 56 C). When splenic cells of mice inoculated with EAC were tested for their natural killer (NK) cell content against YAC-1 target cells, an increase was observed for the first 3 days after inoculation. Plasma lactate dehydrogenase (LDH) was elevated in these mice. Inoculation of ascitic fluid or serum of EAC-bearing mice into normal mice increased plasma LDH activity markedly over normal levels and the elevated activities remained throughout the life of the mice. The possibility that the LDH-elevating agent was responsible for IFN induction was tested by the use of tumor cells which were repeatedly passaged in vitro, a process which eliminates LDH-elevating virus (LDV). Since the inoculation of the passaged cells had no effect on LDH activity (and NK activity) in normal mice, it was concluded that the IFN inducer was LDV which contaminated the EAC and then enhanced the NK activity. N-tropic murine leukemia virus also contaminated EAC, but this virus was not responsible because cultured cells of EAC still shed virus. (25 Refs)

71. INTERFERON: INDUCTION, PRODUCTION AND PHYSICOCHEMICAL PROPERTIES (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Interferon: Induction, Production and Physicochemical Properties (Oncology Overview) Marcus, P I, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923003:; 0B-81/03:77pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Oncology Overview includes the induction and superinduction of interferon in human animal cells. Interferon production in vivo and in vitro, factors enhancing or inhibiting interferon production, and the priming of interferon production by interferon are covered. The purification and physicochemical properties of interferons are also considered. However, the many actions of interferon and interferon inducers are not covered here, as these topics will appear in separate volumes.

72. ON A POSSIBLE MECHANISM OF ACTION OF INTERFERON.

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Z Naturforsch [C]; 36(3):323-325 1981

The effect of interferon on the ESR spectra of RBC treated with ascorbic acid has been investigated. This model system has been chosen since it represents identically the spectra obtained in cases with acute lymphatic leukemia. The data obtained show that small interferon concentrations increase, while larger concentrations decrease the effect produced by ascorbic acid resulting, finally, in the original RBC ESR spectrum. Atomic absorption studies reveal the presence of copper which might be part of the active principle. (Author abstract) (6 Refs)

73. BIOLOGICAL ACTIVITIES AND MODES OF ACTION OF 9-ALPHA-D-ARABINOFURANOSYLADENINE AND 9-ALPHA-D-ARABINOFURANOSYL-8-AZAADENINE.

Bennett LL, Allan PW, Shaddix SC, Shannon WM, Arnett G, Westbrook L, Drach JC, Reinke CM
Biochemistry Res. Dept., Southern Res. Inst., 2000 Ninth Ave. South, Birmingham, AL, 35255
Biochem Pharmacol; 30(16):2325-2332 1981

From earlier studies it is known that 9-alpha-D-arabinofuranosyladenine (alpha-araA) and 9-alpha-D-arabinofuranosyl-8-azaadenine (alpha-ara-8-azaA) have in vitro antiviral activity, are cytotoxic, and are metabolized in mammalian cells to the triphosphates. This study was designed to compare the in vivo antiviral activities of these compounds and their loci of action with those of 9-beta-D-arabinofuranosyladenine (beta-araA). The latter compound selectively inhibits DNA synthesis in intact cells, and its triphosphate is a known inhibitor of DNA polymerases and ribonucleotide reductase. Whereas beta-araA was significantly effective in the treatment of systemic herpes simplex virus Type 1 (HSV-1) infections in mice, alpha-araA and alpha-ara-8-azaA were therapeutically ineffective. Alpha-AraATP at a concentration of approx 1 mM did not inhibit (1) DNA polymerases present in crude extracts of cultured HEp-2 cells; (2) DNA polymerases present in extracts of KB cells; (3) partially purified DNA polymerase-alpha from mouse embryo cells; or (4) DNA polymerases induced by HSV-1 and HSV-2. DNA polymerase-beta from mouse embryo cells was inhibited to a small extent by 10(-4) M alpha-araATP. In contrast, all of these enzymes were inhibited by beta-araATP at a concentration of 10(-5) M (as shown in these or in earlier studies). The reductions of CDP and UDP by ribonucleotide reductase from L1210 cells were not inhibited by alpha-araATP (approx 10(-3) M), whereas beta-araATP produced 70-80% inhibition at this concentration. In cultured HEp-2 cells, alpha-ara-8-azaA inhibited the incorporation of thymidine, uridine, and formate into macromolecules, but it was without effect on the incorporation of adenine and hypoxanthine, and produced marginal inhibition of the incorporation of leucine. alpha-Ara-8-azaA produced a dose-dependent inhibition of the accumulation of [14C]formyl-glycinamide ribonucleotide in HEp-2 cells treated with azaserine and [14C]formate. These results indicate that the alpha-nucleosides inhibit nucleic acid synthesis by mechanisms different from those of beta-ara-A. (Author abstract) (32 Refs)

74. PHYSICAL MAPPING OF DRUG RESISTANCE MUTATIONS DEFINES AN ACTIVE CENTER OF THE HERPES SIMPLEX VIRUS DNA POLYMERASE ENZYME.

Knopf KW, Kaufman ER, Crumpacker C

Medical Res. Council Virology Unit, Univ. Glasgow, Glasgow, Scotland

J Virol; 39(3):746-757 1981

The genome structures of herpes simplex virus Type 1 (HSV-1)/HSV-2 intertypic recombinants have been previously determined by restriction endonuclease analysis, and these recombinants and their parental strains have been employed to demonstrate that mutations within the HSV DNA polymerase locus induce an altered HSV DNA polymerase activity, exhibiting resistant to three inhibitors of DNA polymerase. The viral DNA polymerases induced by two recombinants and their parental strains were purified and shown to possess similar mol wt (142,000 to 144,000) and similar sensitivity to compounds which distinguish viral and cellular DNA polymerases. The HSV DNA polymerases induced by the resistant recombinant and the resistant parental strain were resistant to inhibition by phosphonoacetic acid, acycloguanosine triphosphate, and the 2',3'-dideoxynucleoside triphosphates. The resistant recombinant (R6-34) induced as much acycloguanosine triphosphate as did the sensitive recombinant (R6-26), but viral DNA synthesis in infected cells and the viral DNA polymerase activity were not inhibited. The 2',3'-dideoxynucleoside-triphosphates were effective competitive inhibitors for the HSV DNA polymerase, and the Ki values for the four 2',3'-dideoxynucleoside triphosphates were determined for the four viral DNA polymerases. The polymerases of the resistant recombinant and the resistant parent possessed a much higher Ki for the 2',3'-dideoxynucleoside triphosphates and for phosphonoacetic acid than did the sensitive strains. A 1.3-kilobase-pair region of HSV-1 DNA within the HSV DNA polymerase locus contained mutations which conferred resistance to three DNA polymerase inhibitors. This region of DNA sequences encoded for an amino acid sequence of 42,000 mol wt and defined an active center of the HSV DNA polymerase enzyme. (Author abstract) (29 Refs)

75. ASSOCIATION OF PHENOTYPIC REVERSION OF TRANSFORMED CELLS INDUCED BY INTERFERON WITH MORPHOLOGICAL AND BIOCHEMICAL CHANGES IN THE CYTOSKELETON.

Brouty-Boye D, Cheng YS, Chen LB
Lab. Viral Oncology, Institut de Recherches Scientifiques sur le Cancer, BP 8, 9 4802 Villejuif Cedex, France
Cancer Res; 41(10):4174-4184 1981

The distribution of microfilament bundles, intermediate filaments, microtubules, vinculin plaques, and extracellular fibronectin matrices was examined by indirect immunofluorescence in x-ray-transformed C3H/10T1/2 cells. The transformed phenotype correlated with a lack of actin cables and vinculin-containing plaques. Both interferon-treated and untreated transformed cells displayed a similar distribution of mitochondria, intermediate filaments, microtubules, and fibronectin. Significant qualitative and quantitative differences between the two types of cells were found in the proteins associated with the cytoskeletal framework by two-dimensional gel analysis. (Author abstract) (27 Refs)

76. MECHANISM OF STIMULATION OF NATURAL KILLER-CELL CYTOTOXICITY BY INTERFERON AND AN INTERFERON-INDUCER IN THE RAT.

Flexman JP, Shellam GR
Dept. Microbiology, Univ. Western Australia, Queen Elizabeth II Medical Centre, Nedlands, Western Australia 6009, Australia
Immunology; 44(2):311-320 1981

The interferon-inducer Newcastle disease virus (NDV) was shown to augment cytotoxicity attributable to natural killer (NK) cells in all of the major lymphoid organs of W/Fu rats except the thymus. The levels of interferon isolated from the spleen following NDV inoculation correlated with the increase in splenic cytotoxicity from the same spleen. Spleen-derived interferon was shown to augment splenic cytotoxicity following iv inoculation, and to augment spleen cell cytotoxicity in vitro. Three major peaks of interferon Type I were found in spleen homogenates corresponding to mol wt of greater than 100,000, 29-33,000 and 19-23,000. All these fractions stimulated spleen cell cytotoxicity when tested in vitro. The rapid drop in splenic cytotoxicity 24 hr after NDV inoculation was associated with a rapid fall in interferon levels in vivo. The need for the continued presence of interferon for the stimulation of cytotoxicity was demonstrated when spleen cells pretreated with interferon for 4 hr in vitro lost their augmented cytotoxicity upon culturing for a further 20 hr in the absence of interferon. Although splenic cytotoxicity returned to control levels within 24 hr of a single 107.3 EID50 dose of NDV, repeated doses of NDV maintained augmented cytotoxicity over a longer period. Spleen cells either taken from rats injected with NDV or pretreated in vitro with interferon showed a two-fold increase in the number of cytotoxic cells bound to W/FuG-1 target cells, with no change in the target binding-cell numbers. However, only the cells pretreated with interferon showed an increase in lytic efficiency. (Author abstract) (30 Refs)

77. INDUCTION AND FUNCTION OF 2',5'-OLIGOADENYLATE SYNTHETASE IN DIFFERENTIATION OF MOUSE MYELOID LEUKEMIA CELLS.

Sokawa Y, Nagata K, Ichikawa Y
Dept. Cellular and Molecular Virology, Inst. Virus Res., Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
Exp Cell Res; 135(1):191-197 1981

The activity of 2',5'-oligoadenylate synthetase (2-5A synthetase), known to be induced by interferon, was detected in mouse myeloid leukemic M1 cells only when they differentiated to phagocytic cells after incubation with conditioned medium (CM) from rat embryo cells. However, no interferon activity occurred in culture fluids of CM-treated M1 cells, although some activity was detected in the cell extracts. When anti-interferon serum was added to M1 cell cultures, the induction of 2-5A synthetase by CM was suppressed. These results suggest that CM stimulated the M1 cells to produce a minute amount of interferon, which was responsible for induction of the 2-5A synthetase activity. On the other hand, development of the phagocytic activity of M1 cells could not be influenced by addition of antiserum. Interferon added exogenously per se neither induced phagocytic activity of M1 cells, nor did it enhance the CM-induced differentiation of the cells. Moreover, dexamethasone, which induced differentiation of M1 cells, was not capable of inducing 2-5A synthetase. These results indicate that interferon and/or 2-5A synthetase plays no essential part in the differentiation of M1 cells. (Author abstract) (43 Refs)

78. MECHANISM OF INHIBITION OF EPSTEIN-BARR VIRUS REPLICATION BY PHOSPHONOFORMIC ACID.

Datta AK, Hood RE
Cancer Res. Center, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Virology; 114(1):52-59 1981

The trisodium salt of phosphonoformic acid (PFA) inhibits Epstein-Barr virus (EBV) replication in lymphoblastoid cells at concentrations nontoxic to cellular growth. The synthesis of early antigen (EA) in the infected cells is not affected by the drug under conditions when viral capsid antigen (VCA) and viral DNA synthesis are inhibited to the extent of 75 and 90%, respectively. In vitro studies with partially purified DNA polymerases show that PFA inhibits EBV-associated DNA polymerase to a greater extent than it inhibits alpha- and beta-polymerases. Enzyme kinetic analysis reveals a linear noncompetitive inhibition with four deoxytriphosphates and a typical uncompetitive inhibition with variable concentrations of DNA as substrate at saturating deoxytriphosphate concentrations. The apparent inhibition constant for EBV-associated polymerase was in the range of 2-3 uM. The inhibitory effect is exerted at the pyrophosphate binding site of DNA polymerase. Although productive viral DNA synthesis is completely arrested by the drug, the virus-associated DNA polymerase activity is expressed normally in superinfected Raji cells even in the presence of the drug. We propose that in addition to potential therapeutic value, the compound could b e used as a tool to study some of the restricted early functions of virus in the absence of productive viral DNA synthesis. Induction of viral DNA polymerase can also be used as an additional marker for expression of early viral functions. (Author abstract) (36 Refs)

OTHER RELATED STUDIES

79. ANALOGS OF PYRIMIDINE AND PURINE MONONUCLEOTIDE PRECURSORS AS METABOLIC INHIBITORS.

Golovinsky E, Spassova M
Inst. Molecular Biology, Bulgarian Acad. Sciences, 1113 Sofia, Bulgaria
Pharmacol Ther; 13(3):385-420 1981

Investigations of the synthesis and biochemical mechanisms of action of the precursor analogs are reviewed and their application and the applicability of the trends in this field are discussed. The analogs are considered in a sequence corresponding to the position of the respective precursor in the chain of reactions of the de novo biosynthesis of pyrimidine or purine nucleotides. Analogs of pyrimidine nucleotide precursors are discussed, including those of L-aspartic acid, ureidosuccinic acid, dihydroorotic acid, orotic acid, and orotidine. Precursor antimetabolites in the biosynthesis of purine nucleoside monophosphates are discussed with respect to imidazole analogs of the cyclic precursors in purine biosynthesis de novo, pyrazole analogs of the cyclic precursors, triazole analogs, and tetrazole and triazole analogs of phosphoribosyl-5(4)-aminoimidazole-4(5)-carboxamide. (284 Refs)

80. PRODUCTION OF AN ANTI-TUMOUR CYTOTOXIN BY HUMAN MONOCYTES.

Matthews N
Dept. Medical Microbiology, Welsh Natl. Sch. Medicine, Heath Park, Cardiff Cf4 4XN, Wales
Immunology; 44(1):135-142 1981

Human monocytes incubated in vitro for 20 hr at 37 C release a factor which is cytotoxic to a number of human and murine tumor cell lines: untransformed cells appear to be less susceptible. A similar factor is produced under comparable conditions by myelomonocytic leukemic cells and by macrophages derived from monocytes by in vitro culture for 8 days. Max production of the factor occurred in the presence of fetal calf serum or autologous plasma and endotoxin. The factor is newly synthesized in culture as its production is reduced if the monocytes are treated with cycloheximide or actinomycin D or incubated at lower temperatures. Freshly isolated monocytes do not release the factor on freeze-thaw or hypotonic lysis. The monocyte cytotoxin has apparent mol wt of 34,000 on Ultrogel AcA54 gel filtration and 140,000 on gradient polyacrylamide gel electrophoresis; it has beta2-gamma1 electrophoretic mobility in polyacrylamide gel and does not appear to be C3a or arginase. (Author abstract) (18 Refs)

81. MOLECULAR PHARMACOLOGY PROGRAM.

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Georgetown Med Bull; 34(4):22-23 1981

Nitrogen mustard and nitrosourea destroy cancer tumor cells by interacting directly with their nuclear macromolecules. For clearer understanding of molecular phenomena, which lead to tumor cell death, different projects are under way. One project tries to define mechanism of nitrosourea toxicity in human and murine bone marrow. Another studies interaction of corticosteroids and alkylating agents and has demonstrated that specific nuclear chromatin targets can be sensitized to nitrosourea by preliminary pretreatment with hydrocortisone. Another project examines potential differences between nuclear chromatin structure and function of normal, tumor, and neoplastic cells, which have developed acquired resistance to nuclear-reactant drugs. The most promising study relates to organization of chromatin and chromosomes on a structure framework known as the nuclear matrix and indicates that drug interaction with this matrix may be extremely deleterious to tumor cells. (no Refs)

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EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. EFFECTS OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE ON CHROMOSOMES, DEPENDING UPON THE CELL CYCLE STAGE AT THE TIME OF EXPOSURE.

Moore RC

Biological Res. Unit, Cancer Inst., 481 Little Lonsdale St., Melbourne 3000, Australia

Mutat Res; 83(3):361-374 1981

JU56 cells, derived from the black-tailed wallaby, were exposed to 1-beta-D-arabinofuranosylcytosine (ara-C), and the frequencies and types of chromosomal aberrations were scored in samples of c-metaphase cells collected at consecutive intervals throughout and following the cell cycle, under conditions which prevented cells in their second division following treatment from being included in the samples scored. For cells exposed in G2, both chromatid-type and chromosome-type lesions were observed. A chase with deoxycytidine (CdR) reduced the frequency of these lesions. There was some evidence that the initial lesions were gaps that may later have been converted into true chromosomal breaks. Lesions were produced chiefly at one chromosome location in early G2 and late S cells; the location was not specifically late-replicating. In all samples of cells in S at the time of exposure to ara-C, aberrations were chiefly, but not entirely, of the chromatid type; there was some evidence that their frequency was correlated with the ratio of DNA synthesis in the affected cells at the time of exposure to the drug. G1 cells were not susceptible to damage of ara-C. The level of damage in S cells was not affected by CdR chase. At no stage in the cell cycle did the lesions observed with ara-C imitate those produced by x-rays. (18 Refs)

2. IN VIVO CELL CYCLE PHASE-PREFERENTIAL KILLING OF MURINE FIBROSARCOMA CELLS BY CISPLATIN.

Sigdestad CP, Grdina DJ

Therapeutic Radiology Dept., Univ. Louisville, Radiation Center, 500 S Floyd St., Louisville, KY, 40292

Cancer Treat Rep; 65(9):845-851 1981

Fibrosarcoma cells were separated by centrifugal elutriation. Selected populations enriched in G1-, S-, or G2 + M-phase cells were then injected (10(4) cells) into the tail veins of C3Hf/Kam mice. Twenty min later, 4 mg/kg of cisplatin was injected iv into one half of the animals in each experimental group. Fourteen days later the number of lung colonies was scored, and the surviving fractions were plotted against the elutriator fraction numbers. The results indicated that all phases of the cell cycle were sensitive to cisplatin but that the G1 phase was the most sensitive by a factor of 10. Biphasic dose-response curves were observed for unseparated control, S-phase, and G2 + M-phase tumor cell populations, indicating a resistant cell population. G1 cells, however, had log killing over four decades without the resistant tail. Using this in vivo system, it is concluded that cisplatin kills cells throughout the cell cycle but exhibits preferential killing of G1 tumor cells. (Author abstract) (26 Refs)

3. S PHASE-SPECIFIC SYNTHESIS OF DIHYDROFOLATE REDUCTASE IN CHINESE HAMSTER OVARY CELLS.

Mariani BD, Slate DL, Schimke RT

(c/o Schimke) Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305

Proc Natl Acad Sci USA; 78(8):4985-4989 1981

We investigated the cell cycle modulation of dihydrofolate reductase (DHFR; tetrahydrofolate dehydrogenase, 7,8-dihydroxyfolate: NADP+ oxidoreductase, EC 1.5.1.3) levels in methotrexate-re sistant Chinese hamster ovary cells synchronized by mitotic selection. DNA content and DHFR concentration were analyzed throughout the cell cycle by standard biochemical techniques and by double fluorescence staining utilizing the fluorescence-activated cell sorter. We found an S phase-specific period of DHFR biosynthetic activity. Commencing within hr 2 of S phase and continuing throughout the duration of S phase, there is a 90% increase in DHFR specific activity. This results from an approx 2.5-fold increase in the level of DHFR, while total soluble protein increases 50% during the same period. This increase is the result of new synthesis of DHFR molecules initiated after the cell is physiologically committed to DNA replication. This increase in DHFR activity through S phase parallels the increasing rate of [3H]thymidine incorporation during the same interval. The max peak of DHFR activity is coincident with the max rate of DNA synthesis, both activities occurring during the bulk of DNA replication within the last stages of the 6.5-hr phase. (Author abstract) (26 Refs)

4. INHIBITION OF CELL CYCLE PROGRESSION OF HUMAN PANCREATIC CARCINOMA CELLS IN VITRO BY L-(ALPHAS,5S)-ALPHA-AMINO-3-CHLORO-4,5-DIHYDRO-5 ISOXAZOLEACETIC ACID, ACIVICIN (NSC 163501).

Meck RA, Clubb KJ, Allen LM, Yunis AA

Inst. Cell Analysis, Dept. Oncology, Univ. Miami Sch. Medicine, Miami, FL, 33101

Cancer Res; 41(11,part1):4547-4553 1981

The inhibition of cell cycle progression of a human pancreatic carcinoma line, MiaPaCa-2, by L-(alphaS,5S)-alpha-amino-3-chloro-4,5-dihydro-5 isoxazoleacetic acid (Acivicin), an antimetabolite and glutamine antagonist, was investigated by means of flow cytometry, cell cycle kinetics, and cell enumeration. Flow cytometric criteria for logarithmically growing MiaPaCa-2 cells were established. Logarithmically growing cells exposed to 50 uM Acivicin appeared to markedly reduce their rate of cell cycle progression after they passed a point in later G1 phase of in early S phase. MiaPaCa-2 cells grew in the presence of 50 uM Acivicin with a population-doubling time of approx 74 hr compared to a 20-hr doubling time for controls. The inhibition of cell cycle progression was at least partially reversed by removal of the drug. Based on previous reports of the biochemical mechanisms of Acivicin actions, several additives to the tissue culture medium were tested for their ability to protect MiaPaCa-2 cells from inhibition of cell cycle progression. Those cultures which contained cytidine partially protected the cells from Acivicin. The mechanisms of inhibited growth induced by exposure to Acivicin is likely a complex reaction to the inhibition of several enzyme systems. (Author abstract) (20 Refs)

5. USE OF EXONUCLEASE III TO DETERMINE THE SITE OF STABLE LESIONS IN DEFINED SEQUENCES OF DNA: THE CYCLOBUTANE PYRIMIDINE DIMER AND CIS AND TRANS DICHLORODIAMMINE PLATINUM II EXAMPLES.

Royer-Pokora B, Gordon LK, Haseltine WA

Dept. Pathology, Sidney Farber Cancer Inst., Harvard Medical Sch., 44 Binney St., Boston, MA, 02115

Nucleic Acids Res; 9(18):4595-4609 1981

A method to detect chemically stable lesions in DNA has been developed using Exonuclease III, a double strand specific nuclease, to digest 5'-end labeled DNA. The products, when analyzed on high resolution DNA sequencing gels, reveal the sites of DNA modification. Cyclobutane pyrimidine dimers induced by UV irradiation can be localized by comparison of the fragments produced by Exonuclease III digestion with fragments obtained after digestion of the DNA with UV specific endonuclease. The experiments demonstrate that Exonuclease III stops one base away from the cyclobutane pyrimidine dimers. Similar experiments with cis- and trans-dichlorodiammine-platinum (II) showed that modifications of DNA by these agents also impede Exonuclease III digestion. In general the same stop sites were found for cis- and trans-platinum adducts. They occur at sites of adjacent guanine bases. Additional stop sites were found for cis-platinum at sites of adjacent guanine bases. These results are in agreement with the model that cis-platinum forms intrastrand guanine-guanine dimers, whereas trans-platinum does not. (Author abstract) (31 Refs)

6. EFFECT OF SANGIVAMYCIN AND XYLOSYLADENINE ON THE SYNTHESIS AND METHYLATION OF POLYSOMAL RIBONUCLEIC ACID IN EHRLICH ASCITES CELLS IN VITRO.

Glazer RI, Hartman KD, Cohen OJ

Lab. Medicinal Chemistry and Biology, DTP, DCT, NCI, Building 37, Room 6D28, Bethesda, MD, 20205

Biochem Pharmacol; 30(19):2697-2701 1981

The pyrrolopyrimidine, sangivamycin, and the adenosine analog, xylosyladenine, were examined for their effects on the synthesis and methylation of polysomal RNA in Ehrlich ascites tumor cells in vitro. The synthesis of non-polyriboadenylic acid (non-poly (A)-) and poly(A)-containing RNA was inhibited 50% at concentrations of 7 x 10(-6) M and 3 x 10(-6) M xylosyladenine, respectively, when adenosine deaminase was inhibited with 2'-deoxycoformycin. Sangivamycin inhibited the synthesis of non-poly(A)- and poly(A)RNA by 50% at concentrations of 5 x 10(-5) M and 2 x 10(-5) M respectively. Electrophoretic separation of non-poly(A)RNA into rRNA and tRNA indicated that the inhibitory effects of both drugs were more pronounced on 28S than on 18S rRNA, and that xylosyladenine but not sangivamycin inhibited the synthesis of tRNA. Assessment of the effects of both analogs on the methylation of polysomal RNA revealed that xylosyladenine inhibited the methylation of non-poly(A)- and poly(A)RNA, while sangivamycin only weakly affected the latter species of RNA. Base methylation of the affected species of RNA was inhibited slightly more than 2'-O-methylation by both drugs. These results indicate that sangivamycin is a more selective inhibitor of polysomal RNA in comparison to xylosyladenine under conditions where adenosine deaminase is not a limiting factor. (Author abstract) (24 Refs)

7. METAL MUTAGENS AND CARCINOGENS EFFECTIVELY DISPLACE ACRIDINE ORANGE FROM DNA AS MEASURED BY FLUORESCENCE POLARIZATION.

Richardson CL, Verna J, Schulman GE, Shipp K, Grant AD

Meloy Laboratories, Inc., 6715 Electronic Drive, Springfield, VA, 22151

Environ Mutagen; 3(5):545-553 1981

Investigations were conducted to determine if DNA interactions with nonintercalative agents could be measured in the acridine orange displacement assay, to study the relative DNA reactivity of carcinogenic and noncarcinogenic metals in this system, and to determine if a correlation between DNA binding and mutagenic or carcinogenic effects could be established. Initial studies with cis-dichlorodiammineplatinum (II) (cis-Pt) demonstrated that acridine orange displacement from DNA, as measured by fluorescence polarization, was a direct result of cis-Pt-DNA binding. When the assay was applied to 13 additional metals, a concentration-dependent inhibition of acridine orange-DNA binding was noted. The shapes of the dose-response curves were generally sigmoidal. The interactions of the 13 metals with DNA were observed within 2 min and remained constant over 2 hr, in contrast with cis-Pt interaction which was optimal at 20 hr. Sodium, potassium, and lithium salts required the highest concentration for activity to displace acridine orange, the activities for the carcinogenic/mutagenic metals were substantially lower, and the activities of magnesium and calcium were intermediate. Thus, this assay provides a relative measure of the interaction of metals with DNA, and this DNA reactivity shows a positive correlation with the mutagenic/carcinogenic potential. (35 Refs)

8. REPLICATION OF POLYOMA DNA IN NUCLEI ISOLATED FROM AZIDOCYTIDINE-INHIBITED FIBROBLASTS.

Eliasson R, Pontis E, Reichard P, Eckstein F

Dept. Biochemistry, Medical Nobel Inst. Karolinska Inst., S-104 01 Stockholm, Sweden

J Biol Chem; 256(17):9044-9050 1981

The compound 2'-deoxy-2'-azidocytidine was earlier shown to inhibit the synthesis of DNA (but not RNA or protein) in polyoma virus-infected 3T6 fibroblasts. The diphosphate of azidocytidine is a known inhibitor of ribonucleotide reductase, but deoxyribonucleotide pools of inhibited cells were only marginally affected. Nuclei isolated from the inhibited cells incorporated dNTPs into polyoma DNA at a fairly normal rate with incorporation occurring mainly around the origin of replication. This led to the earlier suggestion that azidocytidine interferes with origin initiation. We now investigate polyoma DNA replication in nuclei isolated after azidocytidine inhibition of cells from a hydroxyurea-resistant cell line that contains an increased activity of ribonucleotide reductase. The nuclei rapidly incorporated labeled dNTPs into polyoma DNA progeny strands which between 10 sec and 15 min grew from an av length of 100 to 1,500 nucleotides. Incorporation initially occurred to a large extent around the origin of replication, but a substantial part of isotope was also recovered more distant from the origin. All strands were elongated at similar rates irrespective of their location. With 5-bromodeoxyuridine triphosphate replacing dTTP, only 28% of the thymine of progeny strands was substituted by bromouracil after 20 sec of incubation. This value increased to 76% after 15 min. These data demonstrate that synthesis in isolated nuclei starts from short primers, preferentially but not exclusively located in the origin region, and suggest that azidocytidine in intact cells inhibits chain elongation and not origin initiation. (Author abstract) (26 Refs)

9. 5-FLUOROURACIL INCORPORATION INTO HUMAN BREAST CARCINOMA RNA CORRELATES WITH CYTOTOXICITY.

Kufe DW, Major PP
Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
J Biol Chem; 256(19):9802-9805 1981

We demonstrate a highly significant relationship (p less than 0.0001) between the incorporation of 5-fluorouracil in total cellular RNA and loss of clonogenic survival of the human MCF-7 breast carcinoma cell line. The extent of 5-fluorouracil incorporation in RNA is concentration- and time-dependent. Identical results are obtained in experiments employing thymidine to bypass the block of thymidylate synthetase and reverse inhibition of DNA synthesis. These studies suggest that the incorporation of 5-fluorouracil in RNA is the major mechanism of cytotoxic action in this human cell line. (Author abstract) (24 Refs)

10. DNA-PROTEIN CROSS-LINKING BY CHROMIUM SALTS.

Fornace AJ, Seres DS, Lechner JF, Harris CC
Lab. Experimental Pathology, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 20205
Chem Biol Interact; 36(3):345-354 1981

DNA-protein cross-links were detected in several types of mammalian cells in culture when they were exposed to chromate salts. The cell types included human bronchial epithelial cells - the apparent cell type of origin of the malignancies reported in chromate workers. The level of cross-linking was proportional to the concentration of chromate used. These cross-links appeared to be persistent since no removal was seen after 12 hr of repair incubation. A low level of DNA single strand breaks (SSB) were also induced after exposure of the cells to chromate but were rejoined after 4 hr of repair incubation. The active form of chromium appears to be the trivalent since chromic but not chromate salts induced DNA-protein cross-links in isolated nuclei. Chromic salts also produced cross-linking between DNA and protein in soln while the hexavalent form was inactive. These data imply that chromate crosses the cell membrane, is reduced to the trivalent form and induces stable linkages of DNA to protein. (Author abstract) (19 Refs)

11. NONSPECIFIC CLEAVAGE OF PHIX174 RFI DEOXYRIBONUCLEIC ACID BY BLEOMYCIN.

Love JD, Liarakos CD, Moses RE
Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
Biochemistry; 20(18):5331-5336 1981

The covalently closed circular duplex DNA of phiX174 underwent progressive conversion to nicked and linear DNA with increasing bleomycin/phiX174 RFI DNA molecule ratios. The formation of linear DNA (a double-strand break) occurred under limited reaction conditions as low as an av of 0.2 single-strand break/phiX174 RFI DNA molecule. As bleomycin-produced linear DNA was further fragmented by bleomycin, a broad distribution of DNA fragments without notable concentrations of unique size was formed. Restriction enzymes PstI and SstII did not generate discrete fragments from bleomycin-produced full-length linear phiX174 DNA, nor did bleomycin cleavage generate discrete fragments from HpaII or PstI digests of phiX174 RFI. These findings suggest that bleomycin does not act at a few specific sites on phiX174 RFI DNA. The single-strand nick appeared to be the preferred site for bleomycin action for a second cleavage in a phiX174 molecule. (Author abstract) (24 Refs)

12. DIFFERENTIAL RESPONSE OF ELUTRIATED 9L CELLS TO TREATMENT WITH 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA.

Hoshino T, Deen DF, Williams ME, Sano Y
Brain Tumor Res. Center, Dept. Neurological Surgery, Sch. Medicine, Univ. California, San Francisco, CA, 94143
Cancer Res; 41(11,part1):4404-4407 1981

Earlier cytokinetic studies using 9L monolayer culture cells showed that cells began accumulating in the G2 phase (4C position in the DNA distribution) within 30 hr after administration of 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml). Most of these cells reached the G2 phase at 48 hr and remained there for another 24 hr. Similar studies using 9L spheroid culture cells show that 9L cells also began to accumulate at the 4C DNA position 30 hr after administration of 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml); however, only one-half of the cells accumulated in the 4C peak during the first 48 hr after treatment, while the other half remained at the 2C position. Those that remained at the 2C peak might correspond to the G0 cells that exist in 9L spheroids. When one-half the cells were in 2C and one-half were in 4C, the spheroids were dissociated using an enzyme cocktail and sorted using centrifugal elutriation. Cells from each elutriated fraction were analyzed for DNA content using flow cytometry and for viability using a colony-forming efficiency assay. Results indicated that in spheroids, 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml) is more effective against noncycling cells and that repopulation is more vigorous in G2-arrested cells, which presumably were cycling at the time of treatment. (Author abstract) (24 Refs)

13. INDUCTION OF GLUCOCORTICOID-RESISTANT VARIANTS IN A MURINE THYMOMA LINE BY ANTITUMOR DRUGS.

Huet-Minkowski M, Gasson JC, Bourgeois S
(c/o Bourgeois) Regulatory Biology Lab., Salk Inst., San Diego, CA, 92183
Cancer Res; 41(11,part1):4540-4546 1981

Several antitumor drugs are shown to be mutagenic in murine thymoma lines: mitomycin C, bleomycin, streptonigrin, Colcemid, and BD40, an analog of ellipticine. Using conditions yielding 3 to 40% cell survival, all five drugs tested increase the frequency of glucocorticoid-resistant variants. Mitomycin C is as efficient as the classical alkylating agents N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate. The other drugs, previously untested for mutagenic activity on mammalian cells, are weak mutagens yielding variants at frequencies one to two orders of magnitude lower than the alkylating agents. All 152 variants obtained result from defects in the glucocorticoid receptor. Variants induced by mitomycin C, streptonigrin, Colcemid, and BD40 have very reduced receptor activity, as measured by dexamethasone binding. In contrast, bleomycin or the combination of mitomycin C and dexamethasone induce a majority of variants having dexamethasone-binding activity comparable to the parental line. However, assays of nuclear transfer capacity and genetic complementation show that these receptors are nonfunctional and may result from point mutations in the gene encoding the glucocorticoid receptor. This study suggests that, in combination therapies, antitumor drugs might induce glucocorticoid-resistant lymphoid cell variants that could be selected by the hormone. (Author abstract) (27 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

14. EFFECT OF LONIDAMINE ON THE ENERGY METABOLISM OF EHRLICH ASCITES TUMOR CELLS.

Floridi A, Paggi MG, D'Atri S, De Martino C, Marcante ML, Silvestrini B, Caputo A
Regina Elena Inst. Cancer Res., Viale Regina Elena 291, 00161 Rome, Italy
Cancer Res; 41(11,part1):4661-4666 1981

The action of Lonidamine [1-(2,4-dichlorobenzyl)-1-H-indazol-3-carboxylic acid] on oxygen consumption and the rate of aerobic and anaerobic lactate production by Ehrlich ascites tumor cells has been investigated. The rate of oxygen consumption decreases exponentially with the increase of Lonidamine concentration, with max inhibition occurring at 0.40 mM Lonidamine. The rate of aerobic lactate production is inhibited to the same extent as is the oxygen consumption. However, the max effect is observed at 0.12 mM Lonidamine, and the decrease is linear with Lonidamine concentration. Anaerobic lactate production is more sensitive to Lonidamine, and complete inhibition can be observed by raising the concentration to 0.6 mM. The possibility that the decrease observed in lactate production was secondary to the inhibition of sodium- and potassium-containing adenosinetriphosphatase was excluded, because the drug has no effect on this enzyme. Mitochondrial adenosinetriphosphatase was not affected. Lonidamine was, however, shown to inhibit the activity of mitochondrially bound hexokinase to approx the same extent as it inhibited aerobic glycolysis (approx 70%). It is concluded that inhibition of the glycolysis of Ehrlich ascites tumor cells by Lonidamine results from an effect of the drug on the mitochondrially bound hexokinase. (Author abstract) (27 Refs)

15. TAXOL INDUCES THE ASSEMBLY OF FREE MICROTUBULES IN LIVING CELLS AND BLOCKS THE ORGANIZING CAPACITY OF THE CENTROSOMES AND KINETOCHORES.

De Brabander M, Geuens G, Nuydens R, Willebrords R, De Mey J
Lab. Oncology, Janssen Pharmaceutica, B-2340 Beerse, Belgium
Proc Natl Acad Sci USA; 78(9,part2):5608-5612 1981

Taxol, a potent promoter of microtubule polymerization in vitro, induces massive assembly of free microtubules in cultured cells as visualized by immunocytochemistry and electron microscopy. The centrosomes and kinetochores largely lost their capacity to organize microtubule assembly, as became evident by the disappearance of the cytoplasmic microtubule complex and the mitotic spindle. The taxol-induced microtubules were partially resistant to nocodazole, an inhibitor of tubulin polymerization. Moreover, taxol induced microtubule assembly in cells pretreated with nocodazole. Increasing the ratio of nocodazole to taxol restored the ability of the centrosomes and kinetochores to specifically induce microtubule assembly in their immediate vicinity. The data suggest that taxol lowers the critical tubulin concentration in vivo as well as in vitro and that the organizing capacity of the microtubule-organizing centers depends on the cytoplasmic polymerization threshold. (Author abstract) (20 Refs)

16. INTERACTION OF 1-(5-PHOSPHO-BETA-D-ARABINOFURANOSYL)-5-SUBSTITUTED URACILS WITH THYMIDYLATE SYNTHETASE: MECHANISM-BASED INHIBITION BY 1-(5-PHOSPHO-BETA-ARABINOSYL)-5-FLUOROURACIL.

Nakayama C, Wataya Y, Santi DV, Saneyoshi M, Ueda T
Faculty Pharmaceutical Sciences, Hokkaido Univ., Sapporo 060, Japan
J Med Chem; 24(10):1161-1165 1981

A number of 1-(5-phospho-beta-D-arabinosyl)-5-substituted-uracils (ara-UMP's) have been examined as inhibitors of dTMP synthetase. As reversible inhibitors, all were substantially less potent than their 2'-deoxyribosyl counterparts. In the presence of 5,10-methylenetetrahydrofolate (CH2-H4folate), ara-FUMP caused a first-order, time-dependent inactivation of the enzyme. At 0 C, kinetic studies indicated a reversible Kd of 3.6 uM for the ara-FUMP-CH2-H4folate complex, and kappa = 0.22 min-1 for the subsequent inactivation. Spectral studies of the complex and its behavior toward protein denaturants demonstrate that its structure and stoichiometry are directly analogous to those which have previously been described for FdUMP. The significance of this finding with regard to prodrugs of ara-FU and the potential of ara-FU as a chemotherapeutic agent are discussed. (Author abstract) (33 Refs)

17. EFFECT OF BROMOCRIPTINE, SOMATOSTATIN, AND OESTRADIOL-17BETA ON HORMONE SECRETION AND ULTRASTRUCTURE OF HUMAN PITUITARY TUMOURS IN VITRO.

Prysor-Jones RA, Kennedy SJ, O'Sullivan JP, Jenkins JS
Dept. Medicine, St. George's Hosp. Medical Sch., London, SW17 ORE, England
Acta Endocrinol (Copenh); 98(1):14-23 1981

The effect of bromocriptine and somatostatin on hormone secretion and the ultrastructure of human pituitary adenomas was studied in vitro. Prolactin secretion was inhibited by bromocriptine in 3 out of 10 prolactin-secreting tumors and in explants from two normal pituitaries. GH secretion was reduced by bromocriptine in four out of six GH-secreting adenomas but was not affected by the drug in the incubations of normal pituitaries. Somatostatin inhibited GH secretion in two out of five pituitary adenomas and the effect was comparable with that of bromocriptine. Incubation of prolactin-secreting adenomas with estradiol for a long as 24 days produced no change in hormone secretion. Examination of tumor explants by electron microscopy showed that somatostatin and bromocriptine produced accumulation of secretion granules but no changes in the secretory organelles. Long term bromocriptine treatment of 'nude' athymic mice bearing xenografts of human pituitary adenomas suppressed hormone secretion and produced some increase in secretion granules but there were no morphological changes in the secretory organelles or other vital structures of the adenoma cells. (Author abstract) (27 Refs)

18. RETINOIDS: NEW DEVELOPMENTS IN THEIR MECHANISM OF ACTION AS RELATED TO CONTROL OF PROLIFERATIVE DISEASES.

Sporn MB
Lab. Chemoprevention, Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

New evidence suggests that retinoids block proliferation induced by polypeptide hormones (PH) or hormone-like agents. Whether the antiproliferative effects of retinoids on epithelial cell differentiation involves modulation of the action of PH is unknown. Retinoids have been shown to have an antagonistic effect on proliferative PH in several disease states, especially malignancy. (15 Refs)

19. (NA+ + K+)-STIMULATED ATPASE OF HUMAN KIDNEY, NORMAL AND ADENOCARCINOMA. PHOSPHORYLATION AND INHIBITION BY ANTITUMOR PROTEINS.

Zaheer A, Singh D, Montgomery R
Dept. Biochemistry, Univ. Iowa, Iowa City, IA, 52242
Biochem Biophys Res Commun; 102(1):86-92 1981

To evaluate the effect of antitumor proteins on metabolism of cultured tumor cells, (Na+ + K+)-stimulated ATPase isolated from normal human kidney and from renal clear cell adenocarcinoma was treated with macromomycin (MM), auromomycin (AM), largomycin (LM), and NSC 327459. MM, LM, and NSC 327459 (all 50 ug/ml) caused 73.4-93.4% inhibition of enzyme purified from adenocarcinoma. LM and NSC 327459 produced 16.5-23.2% inhibition of the enzyme from normal kidney, but MM and AM did not affect normal kidney ATPase. AM was also ineffective against the enzyme from kidney adenocarcinoma. Cyclic AMP (5 uM) caused a 6x stimulation of the rate of phosphorylation of normal enzyme, compared with a 3x increase of phosphorylation rate for the tumor enzyme. Phosphorylation reduced the enzyme activities: the normal ATPase exhibited 28.8% of original activity and the tumor enzyme showed only 19.1%. The normal enzyme was now sensitive to MM inhibition (approx 40% at 10 ug/m). (16 Refs)

20. REDUCTION IN RABBIT SERUM AND PULMONARY ANGIOTENSIN CONVERTING ENZYME ACTIVITY AFTER SUBACUTE BLEOMYCIN TREATMENT.

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Biochem Pharmacol; 30(18):2577-2584 1981

We studied morphological and biochemical alterations in the lungs of rabbits treated sc with bleomycin (5 mg/kg) 3x weekly for 28 days. This treatment produced morphologically evident pulmonary damage characterized by the appearance of ciliated alveolar epithelial cells and endothelial blebs. No change in pulmonary collagen content was evident. Rabbits treated with bleomycin had significantly less pulmonary angiotensin converting enzyme activity than control animals, although no alterations in lung DNA, protein, glycosaminoglycans or hydroxyproline (an index of collagen) were observed. Serum angiotensin converting enzyme activity decreased with repeated bleomycin administration and was reduced by 42, 48 and 65% from control animals 2, 3 and 4 wk, respectively, after the initiation of drug treatment. these data provide biochemical evidence that subacute bleomycin administration damages the pulmonary endothelium in the absence of fibrosis and can reduce the serum activity of angiotensin converting enzyme in rabbits. (Author abstract) (40 Refs)

21. IN VITRO SCREENING OF POTENTIAL ANTI-CANCER CHEMICALS: EFFECT OF PURINE PYRIMIDINE ANALOGUES ON SEED GERMINATION.

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Toxicology; 21(3):251-260 1981

The effect of various purine and pyrimidine analogues on the germination of Cicer arietinum and Escherichia coli dihydrofolate reductase (DHFR) is reported. Initial experiments with adenine, guanine, cytosine, uracil, and thymidine (1 milliM) did not show any effect on germination at 144 hr; their analogues were quite active. Mercaptopurine stimulated germination, xanthine had no effects, and 8-azaadenine, 8-azaguanine, 2,6-diaminopurine, and 2-hydroxypurine were potent inhibitors (83-93% inhibition). 5-Aminouracil, 6-methyluracil, and methylxanthines (eg caffeine, theophylline, theobromine, and uric acid) exhibited lesser (27-44%) inhibitory effects. 5-Fluorouracil blocked germination at 144 hr to about 90%. The effect of these purine and pyrimidine analogues on RNA synthesis, judged by (2-14C)uracil incorporation, is also presented. Cyclic AMP, adenosine, indole-3-acetic acid, and folic acid partially reversed purine and pyrimidine analogue inhibition of germination. Several newly synthesized pyrimidine analogues inhibited germination and RNA synthesis. A close analogy between interference with germination and inhibition of DHFR was observed. (32 Refs)

22. INDUCTION OF DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIA CELLS (HL-60) BY NUCLEOSIDES AND METHOTREXATE.

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JNCI; 67(5):1025-1030 1981

Various purine and pyrimidine analogs and methotrexate were tested to determine whether they induce morphologic and functional myeloid differentiation in HL-60, a human promyelocytic leukemia cell line. Functional maturity was assessed by nitro blue tetrazolium reduction assays. 3-Deazauridine caused nearly all of the cells to differentiate during 6 days of treatment. Pyrazofurin, virazole, puromycin aminonucleoside, and the tricyclic nucleoside 3-amino-1,5-dihydro-5-methyl-1-beta-D-ribofuranosyl 1,4,5, 6,8-pentaazaacenaphthylene induced maturation in 44-64% of the cells, whereas 5-azacytidine, 5-bromo-2'-deoxyuridine, 5-iodo-2'-deoxyuridine, thymidine, and the antimetabolite methotrexate induced maturation in 28-36% of the cells. In terms of effective concentration, the most potent inducer was methotrexate (10(-8) M). The predominant cell types after treatment with all of these compounds were the metamyelocyte and banded neutrophilic granulocyte. (Author abstract) (34 Refs)

23. DIFFERENCE IN EFFECTS OF VINBLASTINE AND VINCRISTINE ON THE DOG PLATELET AGGREGATION.

Takano S
Dept. Pharmacology, Fukushima Medical Coll., Fukushima 960, Japan
Tohoku J Exp Med; 135(1):79-85 1981

The effects of vinblastine (VB) and vincristine (VC) on aggregation and surface alteration of dog platelets were studied. Platelets were obtained from mongrel dogs of approx 10 kg. Platelets (6 x 10(5)/cubic mm plasma) were exposed to varying doses of VB or VC for different periods. At low concentrations (0.2-20 ug/ml), VB increased ADP-induced platelet aggregation but VC had no effect. VB augmentation of aggregation was greatest (46.3% compared with 26.5% for controls) at a VB concentration of 2 ug/ml. Aggregation was depressed to 14.7% by incubation with 100 ug VB/ml for 30 min. Controls showed 31.8% aggregation and VC-treated platelets 29.0%. VB at 100 ug/ml for 30 min produced 46.0% bumpy-form platelets, compared with 30.4% at 100 ug/ml VC. Platelets treated with VB for 15 min did not respond to ADP, while those exposed to VC for 30 min did aggregate. Apparently VC alters platelet surface formation without affecting aggregation capacity, indicating that membrane deformation is not always required for inhibition of aggregation. (8 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

24. NEW ASPECTS IN THE DEVELOPMENT OF CYTOTOXIC-LINKED ESTROGENS FOR THE CONTROL OF BREAST NEOPLASIA.

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Arch Geschwulstforsch; 51(7):643-649 1981

The selection and use of cytotoxic-linked estrogens, which bind to estrogen receptors (ERs) and thereby specifically concentrate in the target tissues including breast neoplasms, are described. The selection of these agents is based upon their binding ability to cytoplasmic ERs, their cytotoxicity against two human breast cancer cell lines (ER+ MCF-7 and ER- Evas-T), and their endocrinologic properties and toxicology. Four epoxide derivatives of 17-beta-estradiol and 17-alpha-estradiol were found to reversibly bind with ER but showed no cytotoxicity against MCF-7 and Evsa-7 cell lines. Nitrogen mustard derivatives of hexestrol, diethylstilbestrol, and estrone displayed binding affinity for ER and cytotoxicity against MCF-7 cells. Only the two mononitrogen mustard derivatives of estrone inhibited growth of Evsa-7 cells. This indicated that these nitrogen mustard derivatives had a weaker effect on the Evsa cell line, consistent with the hypothesis of a participation of ERs in their cytotoxic action. The results indicated that the linking of a cytotoxic group on an estrogen in an appropriate position can yield a drug with a significant binding affinity for ERs. The therapeutic implications of these findings are discussed. (13 Refs)

25. EFFECT OF CIS-DICHLORODIAMMINE PLATINUM II AND X RAYS ON MAMMALIAN CELL SURVIVAL.

Carde P, Laval F
(c/o Laval), Institut de Recherches de Radiobiologie Clinique (INSERM), 94800 Villejuif, France
Int J Radiat Oncol Biol Phys; 7(7):929-933 1981

The influence of cis-dichlorodiammine platinum II (cis-Pt (II)) on the survival of x-irradiated H4 cells derived from a rat hepatoma was studied in an attempt to determine the potential use of this drug to increase the efficiency of radiotherapy. In studies of cis-Pt (II) cytotoxicity, it was found that plateau phase cells were less sensitive to the drug than were exponential cells. When plateau phase cells were incubated for 1 hr with cis-Pt (II) and then irradiated, the survival curves showed modifications both of the extrapolation number and the slope of the curve. The Do decreased from 140 rad for control cells to 135 rad for the cis-Pt (II)-treated cells. Cis-Pt (II) had the same toxicity in both euoxic and hypoxic plateau H4 cells. However, the decrease in Do was more pronounced when plateau cells were treated with cis-Pt (II). The effects of the cis-Pt (II) on the survival curve and Do of exponentially growing H4 cells were insignificant. The repair of sublethal damage (SLD) was measured in exponentially growing H4 cells treated or not treated with cis-Pt (II). Cis-Pt (II) was found to inhibit the repair of SLD. This inhibition was observed only when the drug was present in the medium during the fractionation period. When plateau phase cells were irradiated with 750 rad and then incubated with cis-Pt (II), the survival increase, observed in control cultures, was no longer evident. The results suggested that combined treatment with cis-Pt (II) and ionizing radiations could increase the efficiency of radiation, especially in the case of stationary cells in hypoxia. (20 Refs)

26. FLOWCYTOMETRIC ANALYSIS OF THE EFFECT OF ANTITUMOR DRUGS USING A HUMAN NEUROBLASTOMA MODEL XENOGRAFTED INTO NUDE MICE.

Tsuchida Y, Yokomori K, Saito S, Takakura K, Yamamoto H, Nomura K
Dept. Pediatric Surgery, Faculty Medicine, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan
Shoni Geka; 13(4):517-524 1981

Nude mice bearing human neuroblastoma in the sc tissue were injected ip with cis-platinum 10 mg/kg mouse wt, and changes in the cell cycle of the tumor specimens were studied with flow-cytometry. An increase in S phase cells and in G2 + M phase cells occurred 24-48 hr and 72 hr after the injection, respectively. Nude mice bearing human neuroblastoma were treated more effectively when epipodophyllotoxin was given 72 hr after the treatment with cis-platinum, or when adriamycin was given 36 hr after the treatment with cis-platinum, than when they were treated with the single agent alone. A significant increase in S phase was observed 7 days after subtotal resection of the tumor mass, and adriamycin given 7 days postoperatively was found more effective than that given 14 days postoperatively. (10 Refs) (In JPN)

27. POSTRADIATION DNA REPAIR IN MAMMALIAN CELLS AFTER COMBINED EXPOSURE TO HYPERTHERMIA, 8-BROMOCAFFEINE, AND ACTINOMYCIN D.

Rezvaia SP, Khanson KP
Central Res. Roentgenoradiological Inst., Leningrad, USSR
Radiobiologiia; 21(3):326-329 1981

The effect of combined exposure to hyperthermia, 8-bromocaffeine (BC), and actinomycin D (AD) on DNA repair was studied in irradiated (5,000 rads) LL cells. The level of double-stranded DNA after incubation with BC or AD at 41 C was significantly greater than that at 37 C. These findings indicate that hyperthermia does not enhance the inhibitory effect of BC and AD. (14 Refs) (In RUS)

28. AN ULTRASTRUCTURAL STUDY OF MOUSE LUNG TREATED WITH ISONIAZID (INH) AND ITS ANTITOXICANTS.

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Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay 400 012, India
Indian J Cancer; 18(3):194-197 1981

The pathogenic morphological changes in lung tissue induced by the tuberculostatic drug isonicotinic acid hydrazide (INH) and the protective effects of its antitoxicants were studied in three- and six-wk old male Swiss mice. Animals were injected ip with 0.09 mg INH/g body wt. Some mice were injected ip with L-arginine, L-sodium glutamate, pyridoxine, or folic acid The dose for the amino acids was 0.9 mg/g body wt. The dose for vitamins was 0.45 mg/g body wt. All animals were sacrificed after 24 hr and lung tissue was examined. Normal Type II lung cells were characterized by membrane-bound cytosomes, mitochondria, a few endoplasmic reticulum profiles, small vesicles, one or more Golgi complexes, and multivesicular bodies. Tissues from antitoxicant-treated controls appeared normal. Type II cells from animals treated with INH were enlarged and contained hypertrophied nuclei. Increased chromatin was densely marginated in some cells. Mitochondria were swollen. Ribosomes, multivesicular bodies, and small vesicular bodies were increased. Cytosomes were enlarged and either contained lamellar material or were empty. Type II cells from mice treated with INH plus antitoxicant appeared normal. This suggest that antitoxicants protect vulnerable lung tissue from the effects of INH. (14 Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

29. MEMBRANE AFFINITY AND METABOLISM OF N4-PALMITOYL-1-BETA-D-ARABINOFURANOSYLCYTOSINE INTO CULTURED KB CELLS.

Tsuruo T, Iida H, Hori K, Tsukagoshi S, Sakurai Y
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Cancer Res; 41(11,part1):4484-4488 1981

N4-Palmitoyl-1-beta-D-arabinofuranosylcytosine (N4-palmitoyl-ara-C), a lipophilic derivative of 1-beta-D-arabinofuranosylcytosine, possessed an affinity for KB cell plasma membrane. Approx 15 to 25% of the drug incorporated into KB cells was retained in plasma membrane when the cells were treated with the drug for 1 to 32 hr at 10 uM, the concentration required for 50% inhibition of cell growth. Less than 5.3% of the drug was found in the plasma membrane when the cells were treated with 1-beta-D-arabinofuranosylcytosine. N4-Palmitoyl-ara-C in the membrane fraction cosedimented with plasma membrane in a sucrose density gradient at 4 C, indicating a close association between the drug and the membrane. The affinity of N4-palmitoyl-ara-C for plasma membrane probably contributes to the efficient uptake rate and the strong cytotoxic effect of N4-palmitoyl-ara-C reported previously. The metabolites of N4-palmitoyl-ara-C in KB cells, treated with the drug for 32 hr at the concentration required for 50% inhibition of cell growth (10 uM), were analyzed by diethylaminoethyl Sepharose CL-6B column chromatography and thin-layer and paper chromatography. This analysis showed that over 98% of the drug present in the KB cell was N4-palmitoyl-ara-C. The active metabolites, 1-beta-D-arabinofuranosylcytosine, 1-beta-D-arabinofuranosylcytosine 5'-monophosphate, N4-palmitoyl-1-beta-D-arabinofuranosylcytosine 5'-monophosphate, and 1-beta-D-arabinofuranosylcytosine 5'-triphosphate, were found in amounts of 0.41, 0.37, 0.17, and 0.05%, respectively, of the total drug found in the cells. Also found were the inactive metabolites 1-beta-D-arabinofuranosyluracil and 1-beta-D-arabinofuranosylcytosine diphosphate choline in amounts of 0.61 and 0.29%, respectively. (Author abstract) (27 Refs)

30. IDENTIFICATION OF THE MECHANISM OF ACTIVATION OF 9-BETA-D-ARABINOFURANOSYLADENINE IN HUMAN LYMPHOID CELLS USING MUTANTS DEFICIENT IN NUCLEOSIDE KINASES.

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Cancer Res; 41(11,part1):4478-4483 1981

The biochemical basis of cellular resistance to 9-beta-D-arabinofuranosyladenine (ara-A) and its natural purine derivative, deoxyadenosine, was investigated with two mutants of cultured human T-lymphoblastoid CCRF-CEM cells. One mutant that lacked deoxycytidine kinase activity, designated CEM/ara-C, retained about 10% of wild-type deoxyadenosine kinase and deoxyguanosine kinase activity each but maintained normal adenosine kinase or thymidine kinase activity. This suggested that in these human T-lymphoblastoid cells, as in other previously studied mammalian cells, deoxycytidine and purine deoxyribonucleosides are phosphorylated by the same enzyme. Despite this extensive reduction of purine nucleoside kinase activities, the cytotoxicity of ara-A or deoxyadenosine was not appreciably affected, decreasing by only 2.5-and 6-fold, respectively. A second mutant, isolated by selecting CEM/ara-C mutants that were resistant to ara-A, showed a 100-fold increase in resistance to ara-A cytotoxicity. This ara-A-resistant subline was deficient in the activities of two enzymes, deoxycytidine kinase and adenosine kinase, and showed a high degree of resistance to deoxyadenosine, adenosine, and pyrazofurin but not to pyrimidine analogs, such as 5-fluorodeoxyuridine or 5-fluorouridine. Further studies of ara-A and deoxyadenosine phosphorylation in wild-type and resistant cell lines disclosed that, although deoxycytidine kinase is the principal enzyme for their phosphorylation in vitro, their intracellular conversion to cytotoxic nucleotides depends on the joint action of deoxycytidine kinase and adenosine kinase rather than purine-specific deoxynucleoside kinase, as previously thought. (Author abstract) (27 Refs)

31. DRUG-BINDING MACROMOLECULAR LIPIDS FROM L1210 LEUKEMIA TUMORS.

Taylor RF, Teague LA, Yesair DW
Biomolecular Sciences Section, Arthur D. Little, Inc., Cambridge, Massachusetts, 02140
Cancer Res; 41(11,part1):4316-4323 1981

The isolation and purification of at least two distinct macromolecular lipids from murine L1210 tumors either sensitive or resistant to the terephthalanilide NSC 38280 are described. The lipids are extracted from the tumors with chloroform:methanol and purified utilizing a series of gel permeation and affinity chromatography columns with chloroform:methanol elution. Preliminary characterization of the macromolecular lipids indicates that they have low mol wt (greater than 10,000 but less than 25,000) and are comprised of lipid, carbohydrate, and polyamino components. Significant differences were found between the component composition, molecular size, and column elution properties of the two lipids. One of the macromolecular lipids is extractable from both sensitive and resistant tumors and binds terephthalanilides, Cain quinoliniums, a carbanilide, bis(substituted aminoalkylamino)anthraquinones, and Adriamycin. The other macromolecular lipid appears to occur only in resistant tumors and does not bind the terephthalanilides, Cain quinoliniums, or the carbanilide. Further, the binding studies may predict a correlation between drug binding to the lipids in vitro and drug activity against L1210 leukemia and other tumors in vivo. The polyamine, spermine, also binds to the macromolecular lipids and can displace drugs bound to the lipids. Such spermidine displacement of drug binding is either competitive or noncompetitive in nature depending on the cell line origin of the lipid. The isolated macromolecular lipids may represent components of binding sites for cancer-chemotherapeutic drugs in vivo. (Author abstract) (38 Refs)

32. TAMOXIFEN AZIRIDINES: EFFECTIVE INACTIVATORS OF THE ESTROGEN RECEPTOR.

Robertson DW, Wei LL, Hayes JR, Carlson KE, Katzenellenbogen JA, Katzenellenbogen BS
Dept. Chemistry, Univ. Illinois., Urbana, IL, 61801
Endocrinology; 109(4):1298-1300 1981

Two analogs of the antiestrogen tamoxifen, which bear a chemically reactive aziridine function in place of the dimethylamino group, bind to the estrogen receptor from rat uterus and from MCF-7 human breast cancer cells and appear to react irreversibly with the receptor at the estrogen binding site, in a time-and concentration-dependent fashion. Because these compounds are effective receptor inactivators in uterus and breast cancer cells, they should prove to be useful probes for investigating the role of receptor in regulating cellular responses to estrogen and in studying the dynamics of estrogen receptor synthesis and turnover. (Author abstract) (9 Refs)

33. IDENTIFICATION OF THE METABOLITES OF AN ANTITUMOR TRICYCLIC NUCLEOSIDE (NSC-154020).

Schweinsberg PD, Smith RG, Loo TL
(c/o Loo) Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Biochem Pharmacol; 30(18):2521-2526 1981

The metabolism of 3-amino-1,5-dihydro-5-methyl-1-beta-D-ribofuranosyl-1, 4,5,6,8-pentaazaacenaphthylene (TCN, NSC-154020) was studied in human RBC. With use of high performance liquid chromatography, three metabolites in addition to the major metabolite. TCN 5'-monophosphate, were detected. After isolation and purification of the metabolites, their structures were elucidated by spectrometric methods and incubations with cultured cells and catabolic enzymes. All resulted from the oxidation of TCN. Two are proposed to be alpha- and beta-anomers of a D-ribofuranosyl nucleoside with a pyrimido[4,5-c]pyridazine-4-one base structure. The third metabolite is proposed to be the 5'-monophosphate of the beta-anomer. A mechanism for the oxidation of TCN is presented, but the exact biological oxidant involved remains unclear. (Author abstract) (12 Refs)

34. FACILITATED TRANSPORT OF 6-MERCAPTOPURINE AND 6-THIOGUANINE AND NON-MEDIATED PERMEATION OF 8-AZAGUANINE IN NOVIKOFF RAT HEPATOMA CELLS AND RELATIONSHIP TO INTRACELLULAR PHOSPHORIBOSYLATION.

Plagemann PG, Marz R, Wohlhueter RM, Graff JC, Zylka JM
Dept. Microbiology, Univ. Minnesota, Medical Sch., Minneapolis, MN, 55455
Biochim Biophys Acta; 647(1):49-62 1981

The compound 6-Mercaptopurine and 6-thioguanine strongly inhibited the zero-trans entry of hypoxanthine into Novikoff rat hepatoma cells which lacked hypoxanthine/guanine phosphoribosyltransferase, whereas 8-azaguanine had no significant effect. 6-Mercaptopurine was transported by the hypoxanthine carrier with about the same efficiency as its natural substrates (Michaelis-Menten constant = 372 +-23 uM; max velocity = 30 +-0.7 pmol/ul cell H2O per s). 8-Azaguanine entry into the cells, on the other hand, showed no sign of saturability and was not significantly affected by substrates of the hypoxanthine/guanine carrier. The rate of entry of 8-azaguanine at 10-100 uM amounted to only about 5% of that of hypoxanthine transport and was related to its lipid solubility in the same manner as observed for various substances whose permeation through the plasma membrane is believed to be non-mediated. Only the non-ionized form of 8-azaguanine (pKa = 6.6) permeated the cell membrane. Studies with wild type Novikoff cells showed that permeation into the cell was the main rate-determining step in the conversion of extracellular 8-azaguanine to intracellular aza-GTP and its incorporation into nucleic acids. In contrast, 6-mercaptopurine was rapidly transported into cells and phosphoribosylated; the main rate-determining step in its incorporation into nucleic acids was the further conversion of 6-mercaptopurine riboside 5'-monophosphate. (Author abstract) (35 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

35. INTERACTION OF THE ANTITUMOR DRUG 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE AND RELATED ACRIDINES WITH NUCLEIC ACIDS.

Wilson WR, Baguley BC, Wakelin LP, Waring MJ
Dept. Pathology and Cell Biology, Univ. Auckland Sch. Medicine, Private Bag, Auckland, New Zealand
Mol Pharmacol; 20(2):404-414 1981

The acridine antitumor drug 4'-(9-acridinylamino)methanesulfon-m-anisidide (m-AMSA) is known to be an inhibitor of nucleic acid synthesis. Correlation between m-AMSA (and other related acridine) binding to different nucleic acids (calf thymus) and biological activity and molecular structure were examined using equilibrium dialysis, spectrophotometry, and competition with ethidium. All three techniques indicated an intrinsic association constant of approx 1.5 x 10(5)/M at an ionic strength of 0.01. Increasing ionic strength depressed the association constant by a factor corresponding to that predicted for a monocationic ligand. Binding of m-AMSA was highly selective for native DNA; its affinity for heat-denatured DNA and ribosomal RNA was lower by factors of 5 and 25, respectively. All acridines examined discriminated in favor of DNA Among seven acridines tested, no simple correlation could be found between antitumor potency or selectivity and strength of DNA binding. Presence of an unsubstituted methanesulfonanilide ring did not interfere with binding to double stranded DNA, but addition of a methoxy substituent at the 3' ring position may sterically hinder intercalation of the acridine nucleus of the drug. (36 Refs)

36. ROLE OF ONE-ELECTRON AND TWO-ELECTRON REDUCTION PRODUCTS OF ADRIAMYCIN AND DAUNOMYCIN IN DEOXYRIBONUCLEIC ACID BINDING.

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Biochem Pharmacol; 30(18):2626-2629 1981

Electron spin resonance studies showed that microsomal NADPH activation produced one- and two-electron reduction products (C7-free radical and C7-quinone methide) of adriamycin and daunomycin that bound to DNA and proteins. Formation of two-electron reduction products was also catalyzed by a 105,000 a supernatant fraction. (20 Refs)

37. RETINOIC ACID ANALOGUES WITH RING MODIFICATIONS. SYNTHESIS AND PHARMACOLOGICAL ACTIVITY.

Dawson MI, Hobbs PD, Chan RL, Chao WR

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J Med Chem; 24(10):1214-1223 1981

Analogues of retinoic acid that have their major modifications in the 5,6 double bond and 4-methylene group regions of the beta-cyclogeranylidene ring have been synthesized as potential agents for the treatment and prevention of epithelial cancer. These modifications were intended to reduce retinoid toxicity by lowering the effective treatment dose because the major metabolic deactivation pathway would be inhibited. Ethyl (E)-3,7-dimethyl-9-(exo-2-bicyclo[2.2.1]-heptyl) 2,4,6,8-nonatetraenoate (7) ethyl (E)-3,7-dimethyl-9-(2,2,6-trimethylbicyclo[4.1.0]hept-1 yl)-2,4,6,8-nonatetraenoate (18), (E)-1-(4-carbethoxyphenyl)-2-methyl-4-(2,2,6 trimethylbicyclo[4.1.0]hept-1-yl)-1,3-butadiene (28), (E)-retinoic acid-4,4,18,18,18-d5 (39), and ethyl (E)-3,7-dimethyl-9-(3,3-ethano-2,6,6-trimethyl-1 cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (47) displayed moderate to excellent activity in an assay for the inhibition of tumor promoter-induced mouse epidermal ornithine decarboxylase. (Author abstract) (28 Refs)

EFFECTS OF ANTIMETASTATIC AGENTS

38. INHIBITION OF THE PLATELET-AGGREGATING ACTIVITY OF TWO HUMAN ADENOCARCINOMAS OF THE COLON AND AN ANAPLASTIC MURINE TUMOR WITH A SPECIFIC THROMBIN INHIBITOR, DANSYLARGININE N-(3-ETHYL-1,5-PENTANEDIYL)AMIDE.

Pearlstein E, Ambrogio C, Gasic G, Karpatkin S
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Cancer Res; 41(11,part1):4535-4539 1981

Platelets are required for certain experimental metastases. Several lines of animal tumor cells aggregate platelets in vitro and in vivo. Previous studies with one of these lines, an SV40-transformed 3T3 mouse fibroblast (SV3T3) have revealed that the platelet-aggregating material is an extractable membrane-associated sialolipoprotein which requires divalent cation, complement, and a heat-stable plasma component for activity. Little information is available on the interaction of human tumors with platelets. We now report on the ability of two human adenocarcinomas of the colon (LoVo and HCT-8) and an anaplastic mouse tumor (Hut-20) to aggregate platelets by a different mechanism, the generation of thrombin. These spontaneous cell lines aggregate human or rabbit platelet-rich plasma after a 1-to 2-min lag period. This is often followed by a visible clot. Unlike SV3T3 cells, aggregation by LoVo, HCT-8, and Hut-20 cells is not inhibited by neuraminidase, trypsin, or cobra venom factor. These three cell lines markedly shorten the recalcification time of citrated plasma, whereas SV3T3 cells do not. Phospholipase A2 treatment inhibits the shortening of the recalcification time for the three tumors; this parallels its inhibitory effect on platelet aggregation. LoVo, HCT-8, and Hut-20 cells generate thrombin via the 'tissue factor' coagulation pathway (using coagulation factor-deficient substrates). Dansylarginine-N-(3-ethyl-1,5-pentanediyl)amide, a highly specific, potent antithrombin antagonist, inhibits LoVo-, HCT-8-, and Hut-20-induced platelet aggregation at 4 to 15 uM, whereas its effect on SV3T3 cells is negligible. If platelets are required for certain human tumor metastases, dansylarginine-N-(3-ethyl-1,5-pentanediyl)amide, or other antithrombin agents, may prove to be valuable therapeutic agents. (Author abstract) (37 Refs)

39. EFFECTS OF 5(2-CHLOROBENZYL)-4,5,6,7-TETRAHYDROTHIENO[3,2 C]PYRIDINE HYDROCHLORIDE (TICLOPIDINE), A PLATELET AGGREGATION INHIBITOR, ON BLOOD-BORNE METASTASIS.

Kohga S, Kinjo M, Tanaka H, Ogawa M, Ishihara M, Tanaka N
(c/o Tanaka) Res. Inst., Daiichi Pharmaceutical Co., Edogawa-ku, Tokyo 132, Japan
Cancer Res; 41(11,part1):4710-4714 1981

A new platelet aggregation inhibitor compound, 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2 C]pyridine hydrochloride (ticlopidine), was examined for its inhibitory effects on blood-borne metastasis using three different rodent tumors (B16 melanoma, Lewis lung carcinoma, and rat ascites hepatoma, AH130). Ticlopidine was administered po to the rodents. It inhibited the aggregation of platelets induced by ADP, thrombin, crude extract of AH130, and viable AH130 and B16 melanoma cells and also resulted in a significant decrease of pulmonary metastasis induced by iv injection of B16 melanoma and AH130. Spontaneous pulmonary metastasis of Lewis lung carcinoma was also inhibited by po administration of ticlopidine. This new compound may be a useful agent for inhibiting platelet aggregation caused by various agents and for suppressing hematogenous pulmonary metastasis. (Author abstract) (23 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

40. REDOX POTENTIAL OF IRON-BLEOMYCIN.

Melnyk DL, Horwitz SB, Peisach J
Dept. Molecular Pharmacology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Biochemistry; 20(18):5327-5331 1981

The oxidation-reduction potential of the iron complex of bleomycin, an antitumor agent that cleaves DNA, was measured at 25 C, pH 7.0, by using both a microcoulometric and an optical absorption method. A value of 129 +-12 mV was obtained vs the standard hydrogen electrode for a single-electron process. Thus, ferrous bleomycin, the active form of the antitumor drug, can be regenerated under physiological conditions from ferric bleomycin, a product of the DNA cleavage reaction. (Author abstract) (23 Refs)

INTERFERON AND OTHER ANTIVIRALS

41. INTERFERON-INDUCING AND ANTIVIRAL ACTIVITY OF LEVAMISOLE.

Ershov FI, Grigorian SS, Kremerman IB, Nikolaeva OV
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Antibiotiki; 26(8):617-620 1981

The interferon (IF)-inducing activity of levamisole (LM) was studied in random-bred-albino mice. The peak of IF (320-640 IU/ml) in the blood plasma was recorded 4-6 hr after LM administration (100 mg/kg, po). LM provided a 35-40% protection against tick-borne encephalitis. LM was ineffective against influenza virus. (13 Refs) (In RUS)

42. INTERFERONS, DOUBLE-STRANDED RNA, AND RNA DEGRADATION. ISOLATION AND CHARACTERIZATION OF HOMOGENEOUS HUMAN (2'-5')(A)N SYNTHETASE.

Yang K, Samanta H, Dougherty J, Jayaram B, Broeze R, Lengyel P
Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, CT, 06511
J Biol Chem; 256(17):9324-9328 1981

One of the mediators of interferon action is (2'-5')(A)n synthetase. If activated by double-stranded RNA it converts ATP into pyrophosphate and (2'-5')(A)n. In turn, (2'-5')(A)n activates a latent endoribonuclease (RNase L) which cleaves single-stranded RNA. We report here the isolation and characterization of a homogeneous human (2'-5')(A)n synthetase. The enzyme was purified from interferon-treated HeLa S3 cells by chromatography of a ribosomal salt wash fraction on DEAE-cellulose, poly(I).poly(C) agarose, and CM-cellulose. The purified (2'-5')(A)n synthetase can convert over 90% of ATP into (2'-5')(A)n. The enzyme is unstable but can be stabilized by certain nonionic detergents (eg Triton X-100). Its apparent Mr = 100,000, as determined by gel electrophoresis in sodium dodecyl sulfate, and about 80,000, as determined by centrifugation through a glycerol gradient. The human (2'-5')(A)n synthetase is similar to the corresponding enzyme from mouse Ehrlich ascites tumor cells, but differs from the latter size (100,000 vs 105,000 daltons) and in ionic conditions required for max activity. (Author abstract) (33 Refs)

43. ACCUMULATION OF NEWLY SYNTHESIZED MRNAS IN RESPONSE TO HUMAN FIBROBLAST (BETA) INTERFERON.

Colonno RJ
Central Res. and Development Dept., Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, DE, 19898
Proc Natl Acad Sci USA; 78(8):4763-4766 1981

Treatment of human fibroblast cells with human fibroblast (beta) interferon for up to 8 hr resulted in the accumulation of at least four mRNAs. The mRNAs were isolated from cellular polysomes and characterized by stimulation of translation in a wheat germ cell-free protein synthesis system. The mRNAs appear as early as 2 hr after exposure to interferon and can be translated in vitro into proteins having mol wt of 61,000, 62,000, 64,000, and 68,000. The response is not elicited by mouse interferon or insulin and does not occur in the presence of actinomycin D. Chase experiments indicated that the induced mRNAs remain ribosome-associated for at least 3 hr after their synthesis. The appearance of the induced mRNAs correlated directly with the onset of an antiviral state. Velocity sedimentation of the induced mRNAs on sucrose gradients demonstrated that each of the four induced proteins are encoded by different-sized mRNAs. (Author abstract) (23 Refs)

44. DNA SEQUENCE OF A MAJOR HUMAN LEUKOCYTE INTERFERON GENE.

Lawn RM, Gross M, Houck CM, Franke AE, Gray PV, Goeddel DV
Dept. Molecular Biology, Genentech, Inc., 460 Point San Bruno Blvd., South San Francisco, CA, 94080
Proc Natl Acad Sci USA; 78(9,part2):5435-5439 1981

The gene for human leukocyte interferon alpha2 (designated either LeIF or HuIFN-alpha2) has been isolated from a human genome library. The DNA sequence of this gene demonstrates that it lacks introns. The 3' noncoding sequences of the IFN-alpha2 gene correspond to two types of IFN-alpha2 cDNA clones we have isolated that have alternate sites of polyadenylylation. A comparison of seven human IFN-alpha sequences shows that they are homologous in the 5' flanking region and contain identical 'TATA box' sequences. The recombinant lambda clone containing the IFN-alpha2 gene also contains two copies of the 'Alu family' repeat sequence. (Author abstract) (38 Refs)

45. STRUCTURE OF A CHROMOSOMAL GENE FOR HUMAN INTERFERON BETA.

Ohno S, Taniguchi T
Dept. Biochemistry, Cancer Inst., Japanese Foundation for Cancer Research, Toshima-ku, Tokyo 170, Japan
Proc Natl Acad Sci USA; 78(9,part2):5305-5309 1981

We have cloned and analyzed a chromosomal DNA segment containing the human interferon beta1 gene from a human gene library. The nucleotide sequence of the protein-coding and the noncoding regions of the chromosomal gene was identical to the cDNA sequence reported previously. In the region up-stream from the putative transcription initiation site, significant nucleotide sequence homology was observed between interferon beta1 and alpha1 genes. This region thus may play a role in expression of the interferon genes. From the sequence data and the result of nuclease S1 mapping experiments, we conclude that, like the interferon alpha1 gene, the interferon beta1 gene is devoid of intervening sequences. (Author abstract) (40 Refs)

46. EFFECTS OF HUMAN LYMPHOBLASTOID INTERFERON ON CULTURED BREAST CANCER CELLS.

Shibata H, Taylor-Papadimitriou J

(c/o Taylor-Papadimitriou), Imperial Cancer Res. Fund, Post Office Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

Int J Cancer; 28(4):447-453 1981

The effect of human interferon on growth and fibronectin production in a range of cultured breast cancer cell lines has been investigated. The cell lines differ in their sensitivity to inter feron's growth-inhibitory effect as determined from growth curves, but the degree of sensitivity varies according to the method of assay. When growth was measured in cultures seeded with fairly large numbers of cells, five out of seven lines examined showed a reduction of 50% or more in the number of attached cells after treatment for 8 days with 1,000 units/ml of interferon. Growth of the two cell lines least affected by interferon treatment in dense culture could, however, be markedly inhibited under conditions of clonal growth in agar or when sparsely seeded on plastic and this was due to inhibition of initiation of growth. In some breast epithelial lines, where the number of attached cells was regulated in part by cell shedding, it was found that interferon not only inhibited cell proliferation, but also increased cell shedding. To determine if interferon increased cell shedding by affecting fibronectin production, the total and cell associated fibronectin was estimated in control and interferon-treated cultures. Four of 10 cell lines examined produced detectable amounts of fibronectin, and in only 1 of these lines, Hs578T derived from a carcinosarcoma, was the production and retention of fibronectin inhibited by interferon treatment. In those breast carcinoma lines which produced detectable amounts of fibronectin, the level of production and retention of the protein, expressed as a proportion of the total protein, did not change after interferon treatment, but showed an increase if expressed on a per cell basis. This is explained by the fact that the interferon-treated cells showed an increase in cell vol. (Author abstract) (36 Refs)

47. ANTIVIRAL AND ANTICELLULAR ACTIVITY OF HUMAN LEUKOCYTE AND FIBROBLAST INTERFERONS IN HOMOLOGOUS AND HETEROLOGOUS CELLS.

Orlova TG, Zhdanova LV, Timofeev IV, Indikova IN, Mentkevich LM, Malinovskaia VV, Balandin IG, Kuznetsov VP

N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR

Vopr Virusol; (4):404-407 1981

The antiviral and antiproliferative activities of human WBC and fibroblast interferons (IFs) were tested in human and cattle embryo tracheal cells. The activity of the WBC IF in the homologous cells was similar to that in the heterologous cells. The fibroblast IF was active in the homologous cells but failed to produce antiviral or antiproliferative effects in the heterologous cells. (18 Refs) (In RUS)

48. ELEVATED LEVELS OF (2'-5')OLIGOADENYLIC ACID POLYMERASE ACTIVITY IN GROWTH-ARRESTED HUMAN LYMPHOBLASTOID NAMALVA CELLS.

Krishnan I, Baglioni C

Imperial Cancer Res. Fund, Lincoln's Inn Field, London WC2A 3PX, England

Mol Cell Biol; 1(10):932-938 1981

The relationship between growth status and activity level of (2'-5')oligoadenylic acid polymerase ((2'-5')An polymerase) was studied in human lymphoblastoid cells of the Namalva line under different conditions. The amount of (2'-5')An polymerase formed in an incubation with cell extract was a result of the balance between the synthesis and degradation of (2'-5')An. Degradation of (2'-5')An was almost completely prevented by 10 milliM ATP. A relationship between (2'-5')An synthesis and cell density was observed. A possible relationship between growth status and (2'-5')An polymerase activity was suggested. (2'-5')An polymerase activity seemed to decrease only when Namalva cells were actively proliferating. When cells were cultured with medium containing 0.2% serum, synthesis of DNA declined rapidly, while polymerase activity increased several-fold. (2'-5')An polymerase degradative activity was studied. Changes in (2'-5')An polymerase activity in Namalva cells did not seem to be mediated by interferon. Results indicated that the activity level of (2'-5')An polymerase in Namalva cells is largely determined by the growth status of the cells, since growth-arrested cells displayed an increased polymerase activity. The regulatory mechanism is apparently not activated by interferon. (24 Refs)

49. THE DUAL INTERACTION OF PROSTAGLANDIN E2 (PGE2) AND INTERFERON (IFN) ON NK LYTIC ACTIVATION: ENHANCED CAPACITY OF EFFECTOR-TARGET LYTIC INTERACTIONS (RECYCLING) AND BLOCKAGE OF PRE-NK CELL RECRUITMENT.

Targan SR

Dept. Medicine, Div. Gastroenterology, Univ. California Los Angeles Center for Health Sciences, Los Angeles, CA, 90024

J Immunol; 127(4):1424-1428 1981

In this study we addressed the question of whether the known NK activators prostaglandin E2 (PGE2) and interferon (IFN) can synergistically activate NK lysis and whether they potentiate the same or different subsets of NK cells. We demonstrated that the activation of NK lysis can be enhanced as well as blocked by the interaction of these two activators. The enhancement of activation was not due to recruitment of separate subsets of pre-NK cells, but rather the synergistic enhancement of the recycling capabilities of the same set of NK cells. There was a temporal relationship to this enhancement. That is, if PGE2 was added during cellular processing required for full expression of NK activation induced by IFN, pre-NK lytic potential was inhibited. If, on the other hand, PGE2 is added after completion of full expression of the IFN-induced activated lytic process, there is enhancement of recycling capabilities of the same number of NK cells. (Author abstract) (18 Refs)

50. EFFECTS OF HYDROCORTISONE ON THE SYNTHESIS OF EPSTEIN-BARR VIRUS ANTIGENS IN P3HR-1 CELLS.

Prachova K, Roubal J
Dept. Experimental Virology, Inst. Sera and Vaccines, 181 03 Prague, Czechoslovakia

Acta Virol (Praha); 25(3):163-166 1981

Hydrocortisone was capable of enhancing the synthesis of Epstein-Barr virus antigens in producer P3HR-1 cells which had been induced with a 24-hr pulse of 5-iodo-2-deoxyuridine. The effect of hydrocortisone was time dependent, suggesting that an early step in the induction process, and not the antigen synthesis itself, was influenced by the drug. (Author abstract) (10 Refs)

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OTHER RELATED STUDIES

51. MECHANISMS OF TOLERANCE TO DNA LESIONS IN MAMMALIAN CELLS.

Meneghini R, Menck CF, Schumacher RI
Dept. Biochemistry, Inst. Chemistry, Univ. Sao Paulo, C.P. 20780, Sao Paulo, Brazil

Q Rev Biophys; 14(3):381-432 1981

The way in which mammalian cells deal with a large burden of unexcised DNA lesions is discussed. The biological consequences of unexcised DNA lesions are considered in terms of cell killing, cell mutation, cell transformation, enhanced virus reactivation, and sister chromatid exchanges. These different biological effects seem to be triggered during DNA replication. Thus, the damaged template has to be replicated in order for the chain of events leading to a certain effect to be initiated. DNA replication on a damaged template is discussed in relation to information from bacterial systems, DNA containing lesions replicated in mammalian cells, effect of template-strand lesions on the rate of DNA synthesis and the structure of the daughter strand, inhibition of replication fork by lesions in the template strand, DNA synthesis along the lesions (postreplication repair), and mechanisms of postreplication repair (recombination, branch migration, 'translesion synthesis', and relief of blocked sites by joining of adjacent replicons). Hints of the inducibility of tolerance to DNA lesions come from distinct approaches such as the enhancement of DNA chain elongation, recovery of the rate of DNA synthesis, recovery in survival, enhanced virus reactivation, and induction of proteins by DNA-damaging agents. (163 Refs)

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EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. DIFFERENTIAL CHROMATID DAMAGE INDUCED BY 6-THIOGUANINE IN CHO CELLS.

Maybaum J, Mandel HG
Dept. Pharmacology, George Washington Univ. Medical Center, Washington, DC, 20037
Exp Cell Res; 135(2):465-468 1981

Treatment of Chinese hamster ovary cells with 6-thioguanine (TG) produces severely disrupted chromatin in G2 cells, as visualized with premature chromosome condensation. In many regions of the chromosome this damage, appearing as a gapped or diffusely staining region, occurs in only one of the sister chromatids. This morphology strongly supports previous reports that TG-induced cytotoxicity is related to its incorporation into DNA and that this lesion is expressed in the cell cycle following that in which drug exposure occurs. (Author abstract) (15 Refs)

2. EFFECTS OF PULSE AND CONTINUOUS INTRAVENOUS INFUSION OF CIS-DIAMMINEDICHLOROPLATINUM ON L1210 LEUKEMIA IN VIVO.

Moran RE, Straus MJ
Div. Neoplastic Diseases, Dept. Medicine and Biochemistry, New York Medical Coll., Valhalla, NY, 10595
Cancer Res; 41(12):4993-4996 1981

The in vivo effects of cis-diamminedichloroplatinum on L1210 leukemia were determined using DNA content distribution analysis by flow microfluorometry and pulse $[^3H]$thymidine labeling indices. Pulse and continuous infusion schedules were investigated. Pulse cis-diamminedichloroplatinum (2 and 6 mg/kg) resulted in progression delay of cells in S and G2 phases and at higher doses (greater than or equal to 12 mg/kg) in G1 as well. Equivalent total doses administered by continuous infusion over 24 to 72 hr delayed cells in G2 with little apparent affect on G1 or S progression. A max survival of 70% increased life span over controls was achieved with a 12-mg/kg pulse. Infusion doses at least 2-fold higher were required to achieve similar increases in survival. Cell cycle changes did not predict for therapeutic benefit, suggesting that, at suboptimal doses, cells were capable of repair. The therapeutic index for both modes of administration was narrow. (Author abstract) (17 Refs)

3. THE ROLE OF DNA REPAIR IN THE RECOVERY OF HUMAN CELLS FROM CISPLATIN TOXICITY.

Pera MF, Rawlings CJ, Roberts JJ
Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England
Chem Biol Interact; 37(1):245-261 1981

In order to better understand the factors that determine the sensitivity of human cells to the antitumor agent cisplatin, we evaluated the capacity of human cells to recover from the cytotoxic effects of this drug and we studied the relationship between biological recovery and DNA excision repair. Normal human fibroblasts were grown to confluence and treated with cisplatin. The cells were then harvested following treatment for measurement of toxicity and extent of DNA reaction, or they were held at confluence in the non-dividing state for periods of up to 7 days. At each time point, cell survival was measured by colony forming efficiency, the amount of platinum bound to DNA was determined by atomic absorption spectrometry, DNA-protein cross-links were measured by alkaline elution and DNA-DNA interstrand cross-links were estimated by both alkaline elution and measurement of renaturable DNA in cell lysates. During post-treatment incubation, minimal DNA synthesis occurred and the cloning efficiency of treated cells rose from approx 1% of control values immediately after treatment, to approx 30% 6-7 days later. Platinum residues were removed from DNA by a first-order process with a half-life of 2.5 days. DNA-DNA interstrand cross-links, which constituted a minority of overall DNA reactions, were lost at a somewhat faster rate ($t_{1/2}$, about 1.5 days). The loss of cross-links was attributed to repair, because DNA degradation was shown to be insignificant following posttreatment incubation. DNA-protein cross-links were lost at a rate similar to that of interstrand crosslink removal. The data show that human cells can recover from cisplatin toxicity and that, during recovery, cells repair interstrand cross-links and remove platinum adducts from DNA. These findings suggest that cytotoxicity is a function of the amount of damage remaining in DNA at the time that cells enter the proliferative cycle. (Author abstract) (29 Refs)

4. THE ROLE OF DNA EXCISION REPAIR IN THE RECOVERY OF HUMAN CELLS FROM CISPLATIN TOXICITY (MEETING ABSTRACT).

Pera MF, Roberts JJ
No affiliation given
Br J Cancer; 43(5):732 1981

We evaluated the capacity of human cells to recover from the cytotoxic effects of the antitumor agent cisplatin, and we studied the relationship between biological recovery and DNA excision repair. Normal human fibroblasts were grown to confluence and treated with cisplatin. The treated cells were then plated immediately, or they were held in the density-inhibited, non-dividing state for various x after treatment. Cells plated immediately after a 1 hr exposure to 40 uM cisplatin showed a survival, measured by colony-forming efficiency, that was 0.21-1.0% of control values. If the cells were held in a density-inhibited state after treatment, no DNA synthesis occurred and survival increased during a 6-day holding period to levels approx 15-40% of controls. During the holding period, nondividing cells removed platinum residues from their DNA by a first-order process with a half-life of 2.5 days. The relationship between the logarithm of cell survival and binding of platinum to DNA was determined for cultures plated immediately after drug treatment, and it was found to be similar to that observed for cells that were held in the non-dividing state and allowed to perform DNA repair prior to plating and entry into the proliferative cycle. DNA-DNA interstrand crosslinks, measured by determination of the renaturable fraction of DNA in cell lysates, appeared to be removed at a rate comparable to that of overall adduct removal. These results show that human cells can recover from the cytotoxic effects of cisplatin, that this biological recovery is related to DNA excision repair and interstrand crosslink removal, and that the determinant of cytotoxicity is the extent of drug-DNA interaction of the time cells undergo DNA synthesis and division. (no Refs)

5. INHIBITORY EFFECTS OF ANTI-NEOPLASTIC PLATINUM COMPLEXES ON DNA AND RNA POLYMERASES (MEETING ABSTRACT).

Kohl HH, Miller DL
Chemistry Department, Auburn University, Auburn, AL, 36849
Clin Chem; 27(6):1066 1981

The present work studies the inhibitory actions of cis-diaminedichloroplatinum II (cis-DDP), trans-diaminedichloroplatinum II (trans-DDP) and other more recently synthesized platinum complexes on both DNA and DNA-dependent RNA polymerases. Soluble and purified enzymes from Escherichia coli were studied in the presence of either a calf thymus DNA template or Poly (dA-dT). We have also studied a completely mammalian transcription system (intact rat liver nuclei) in a DNA-dependent RNA polymerase assay. Measurements of RNA transcription were made using radioactive guanosine triphosphate while those of DNA synthesis utilized tritiated thymidine triphosphate. Incorporation of radioactivity was measured by counting glass fiber filters using liquid scintillation. Our data indicates that the trans-DDP is far more potent than cis-DDP in inhibiting RNA transcription. Ninety percent inhibition was seen using 10 uM trans-DDP while less than 5% inhibition was seen using cis-DDP. The inhibitions of RNA transcription appear to be due to effects on the polymerase enzyme rather than to effects on the DNA template. DNA synthesis, however, appeared to be inhibited by effects on both the enzyme and the nucleic acid template. (no Refs)

6. SODIUM BUTYRATE BLOCKS HELA CELLS PREFERENTIALLY IN EARLY G1 PHASE OF THE CELL CYCLE.

Xue S, Rao PN
Dept. Biology, Beijing Normal Univ., Beijing, People's Republic of China
J Cell Sci; 51:163-171 1981

The effects of sodium butyrate on the cell-cycle traverse of HeLa cells was re-examined using the kinetic and the premature chromosome condensation methods of cell-cycle analysis. The results of this study indicate that the sodium butyrate effects are dose-dependent and cell-cycle phase-specific. Cells in the early G1 period are the most sensitive to the inhibitory effects of the drug. When HeLa cells in exponential growth were exposed to a 5 mM concentration of butyrate for 48 hr, 67% of the cell population was preferentially arrested in the early G1 period as indicated by the condensed morphology of the prematurely condensed chromosomes (PCC). There was no accumulation of cells in the G2 period. The results of this study suggest that hyperacetylation of histones induced by sodium butyrate does not necessarily result in decondensation of chromatin and the butyrate-enhanced protein, which has been reported to be present in butyrate-treated cells, may have a role in the regulation of the transition of cells from early G1 to the subsequent phases of the cell cycle. (Author abstract) (22 Refs)

7. SOME EFFECTS OF TREATMENT OF HEN ERYTHROCYTES IN VITRO WITH N-METHYL-N-NITROSOUREA.

Ward TH, Itzhaki RF
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
J Cell Sci; 51:153-162 1981

Studies have been made of the effect of N-methyl-N-nitrosourea on hen RBC in vitro. These were done to find whether the highly condensed state of the chromatin and the very low metabolic activity of these cells would affect the extent of methylation of the DNA and chromatin proteins and the persistence of any methylation sites in these macromolecules with time after treatment. Also, the effect of methylnitrosourea on incorporation of [3H]uridine into RNA has been examined. It has been found that the DNA, histones and non-histone proteins are methylated. The main methylation site in DNA is 7-methylguanine and its level is higher that that found by others in the DNA of other cell types after treatment with methylnitrosourea; however, methylation of the two types of protein (especially the histones) is relatively very low. The level of methylation decreases in the DNA and the chromatin proteins with time after treatment. The amount of [3H]uridine in RNA was found to decrease after the treatment. (Author abstract) (19 Refs)

8. ALKALINE ELUTION STUDIES WITH BUSULPHAN AND RELATED DIAL-KANESULPHONATES (MEETING ABSTRACT).

Bedford P, Fox BW
Christie Hosptial and Holt Radium Institute, Manchester M20 9BX, England
Br J Cancer; 43(5):733 1981

The two agents, methylene dimethanesulphonate (MDMS) and 1,4-dimethylsulphonyl-oxybutane (busulphan) have been compared in this study. Both agents were found to produce DNA-DNA interstrand crosslinks in cells derived from the transplantable Yoshida rodent sarcoma. In addition, a substantial number of DNA-protein crosslinks and a small number of single-strand breaks were observed after MDMS treatment. The DNA-protein component of crosslinking was entirely attributed to the formaldehyde produced on hydrolysis of the drug. The approx relative occurrence of the observed lesions as a percentage of total damage after MDMS was calculated as 26%, 64% and 10% respectively for DNA-DNA cross-links, DNA-protein cross-links and single-strand breaks. At doses producing 50% cell death in the cross-sensitive YS line, MDMS was found to induce 0.13 cross-links/10(9) dalton compared with 0.151 cross-links/10(9) dalton after an equitoxic dose of busulphan. Initial temporal studies with each agent, using a cell line resistant to MDMS (YR8) and resistant to busulphan (YBUSR) compared with the wild-type YS line, suggested that a saturation of excision repair of the cross-links could occur at high doses of each agent in the sensitive line, whereas this was not the case at equivalent doses in the resistant lines. (1 Ref)

9. INTERACTION OF VP 16-213 WITH DNA REPAIR ANTAGONISTS (MEETING ABSTRACT).

Arnold AM, Whitehouse JM
CRC Medical Oncology Unit, Southampton, England
Br J Cancer; 43(5):733 1981

The podophyllotoxin derivative VP 16-213 can apparently cause single-stranded breaks in DNA, capable of repair. Several compounds are known to be powerful inhibitors of DNA repair, so it was of interest to study the interactions of VP 16-213 with chloroquine and caffeine. Female DBA mice weighing 20 g were inoculated sc with 10(5) TLX lymphoma cells. Three days after inoculation the animals were treated with VP 16-213, together with either chloroquine (20-40 mg/kg) by ip injection or caffeine (0.125-1%) added to the drinking water. By way of a control, vincristine, a drug not thought to damage DNA, was also tested with chloroquine. Results were expressed as increased lifespan (ILS) over untreated controls. VP 16-213 alone (6.25 mg/kg and 12.5 mg/kg) produced an ILS of 9% and 30% respectively. VP 16-213 in the same doses but together with 40 mg/kg chloroquine produced ILS of 78% and 76% respectively. By contrast chloroquine did not enhance the effect of vincristine. One per cent caffeine added to drinking water of animals given VP 16-213 produced a significant but less marked ILS. These preliminary observations provide further evidence that the mode of action of VP 16-213 may be due to the formation of single-stranded breaks in DNA, though it is possible that other mechanisms may be responsible for the apparent synergism. (no Refs)

10. MODE OF ACTION STUDIES OF THE ANTITUMOR ANTIBIOTIC TOROMYCIN AND THE RELATED COMPOUND CHRYSOMYCIN (MEETING ABSTRACT).

Wei TT, Byrne K, Elespuru R, Greenstein M, Pickle D, Richardson C, Stroshane R, Weiss U, White RJ
Frederick Cancer Research Center, Frederick, MD
Program and Abstracts of the 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, November 4-6, 1981, Chicago, Illinois American Society for Microbiology; 1981

The mechanism of action of toromycin, a new antitumor antibiotic, and the closely related compound chrysomycin was investigated. Macromolecular synthesis studies in Bacillus subtilis indicated that upon addition of toromycin or chrysomycin, nucleic acid synthesis was inhibited preferentially to protein synthesis. In particular, inhibition of DNA synthesis was more complete than RNA synthesis. Both toromycin and chrysomycin demonstrated strong activity in the biochemical prophage induction assay (BIA), a sensitive test for agents interacting with DNA. Interaction of these compounds with DNA in vitro was detected by an acridine orange competitive fluorescence polarization assay. Agarose gel electrophoresis of supercoiled DNA indicated that toromycin binds by intercalation at concentrations less than 5 ug/m/. Our data suggest that drug interaction with DNA plays a prominent role in the biological activity of this new type of antitumor antibiotic. (no Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

11. POSSIBLE REQUIREMENT OF INTERNALIZATION IN THE MECHANISM OF IN VITRO CYTOTOXICITY IN TUMOR NECROSIS SERUM.

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Dept. Molecular Biology, Wellcome Res. Lab., Res. Triangle Park, NC, 27709
Cancer Res; 41(12):4885-4890 1981

The mechanism of in vitro cytotoxicity by tumor necrosis serum (TNS) and a purified fraction was examined using sensitive L-M cells. Cell death was assessed by uptake of the dye trypan blue and/or by release of radiolabeled chromium. Cell killing was time and dose dependent. Cell survival was assessed by counting the number of survivors via their ability to internalize the dye neutral red and/or by adherent cell protein. The cytotoxin was not cytostatic. Survival was found to be inversely proportional to cell death. The change in survival was used to estimate the number of cells killed. The number of cells killed was logarithmically related to the amount of toxin. The ability to kill a fixed number of cells was inversely related to the number of cells in the assay well. It was estimated that, at ideal cell seed numbers, 1 ug of TNS protein per 250 ul killed about 50,000 cells in a 20-hr period. Sensitivity was equated with the amount of TNS required to kill 35,000 cells in 20 hr. Inhibitors of RNA and protein synthesis and also elevated temperatures enhanced sensitivity. The combined treatment of 1 uM actinomycin D and 40 C enhanced sensitivity by 15-fold. Resistant normal and tumorigenic cell lines (including human) were rendered sensitive by concomitantly treating them with TNS and cycloheximide or actinomycin D. Cytoskeletal-disrupting agents (colchicine, Colcemid and cytochalasin B), inhibitors of lysosome activity (chloroquine, methylamine, and leupeptin), and 32 C all depressed sensitivity. Sensitivity was nearly equivalent in calcium-free medium. Results substituting partially purified cytotoxin were similar. The results suggest that a toxic factor(s) may need to be internalized and that lysosomal activity may be necessary for cell killing. Comparisons with lymphotoxin are discussed. (Author abstract) (41 Refs)

12. AN UPDATE ON THE BIOCHEMISTRY OF 5-FLUOROURACIL.

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Cancer Treat Rev; 8(3):157-167 1981

Biological activation of 5-fluorouracil (5-FU) depends on the operation of anabolic, catabolic, and target enzymes. Anabolic enzymes acting on 5-FU include uridine phosphorylase, thymidine phosphorylase, phosphoribosyl transferase, uridine kinase, thymidine kinase, ribonucleotide reductase, pyrimidine monophosphate kinase, and pyrimidine nucleoside diphosphate kinase. Catabolic en zymes include those that break down 5-FU and those that break down its anabolites. The uracil-degradative pathway hydrolyzes the pyrimidine ring to beta-ureidopropionic acid and then to beta-alanine. Catabolic enzymes operate at a high rate in the liver, possibly preventing the toxicity of 5-FU. Catabolism of 5-FU is much slower in most tumor cells and is probably not the main mechanism for controlling 5-FU in tumor cells. Phosphatases control various phosphorylated intermediates in 5-FU metabolism. They may be involved in the susceptibility of some tumors to 5-FU. The effect of 5-FU on DNA synthesis involves the action of 5-FU on the target enzymes thymidylate synthetase and the RNA polymerases with the incorporation of 5-FU into RNA. (60 Refs)

13. STIMULATION BY ADRIAMYCIN OF RAT HEART AND LIVER MICROSOMAL NADPH-DEPENDENT LIPID PEROXIDATION.

Mimnaugh EG, Trush MA, Gram TE
Lab. Medicinal Chemistry and Biology, NCI, Building 37, Room 6D28, Bethesda, MD, 20205
Biochem Pharmacol; 30(20):2797-2804 1981

Rat liver and heart microsomes catalyze the transfer of single electrons from NADPH to adriamycin forming semiquinone radicals which, in turn, activate molecular oxygen. This process stimulated lipid peroxidation five- to seven-fold as measured by malonaldehyde formation. Adriamycin-augmented lipid peroxidation was linear with time to 60 min, optimal at 1.0 mg of microsomal protein/ml and pH 7.5, and was proportional to the adriamycin concentration up to 100 uM. An NADPH-generating system was superior to NADPH, and an oxygen atmosphere tripled the rate of peroxidation as compared to air. Nitrogen abolished adriamycin-stimulated peroxidation. Superoxide dismutase, reduced glutathione, alpha-tocopherol, EDTA, dioxopiperazinylpropane (ICRF-187), and dimethylurea were effective inhibitors of lipid peroxidation. This suggests that superoxide anion and possibly hydroxyl radical may be formed by the oxidation of the adriamycin semiquinone radical and thus stimulate the peroxidation of microsomal unsaturated fatty acids. Although adriamycin failed to stimulate lipid peroxidation in heart microsomes from control animals, peroxidation was dramatically increased when adriamycin was added to cardiac microsomes from alpha-tocopherol-deficient rats. Lipid peroxidation in alpha-tocopherol-deficient liver microsomes was 4x greater than in control microsomes with the NADPH-generating system, and adriamycin did not further increase that high rate of peroxidation; however, when NADPH was used as the source of electrons in place of the NADPH-generating system, adriamycin stimulated peroxidation more than two-fold. These results suggest that microsomal lipid peroxidation may play a role in the cytotoxicity and cardiotoxicity of adriamycin. (Author abstract) (46 Refs)

14. ACTION OF MISONIDAZOLE ON L5178Y-R AND L5178Y-S CELLS: II. CYTOTOXICITY AND RADIOSENSITIZATION UNDER HYPOXIC CONDITIONS.

Niepokojczycka E, Szumiel I, Walicka M
Inst. Nuclear Res., 03-195 Warszawa, Poland
Neoplasma; 28(4):435-440 1981

Misonidazole exerts an equal cytotoxic effect on L5178Y-R and L5178Y-S cells: 5 mM misonidazole sensitizes cells of both strains to a similar extent under hypoxic conditions: the effect of drug is 59% of the oxygen effect in L5178Y-R cells and 52% in L5178Y-S cells. It was previously reported that the amount of initial DNA damage determined by the alkaline unwinding technique is 1.3 x lower in irradiated hypoxic L5178Y-R cells than in L5178Y-S cells. Hence it seems that the drug ability to sensitize these cell strains does not depend on amount of initial DNA damage available for interaction. Although the examined L5178Y strains differ in radiosensitivity, their ability to repair oxygen and misonidazole-dependent cellular damage is similar. (Author abstract) (20 Refs)

15. ACTION OF MISONIDAZOLE ON L5178Y-R AND L5178Y-S CELLS. I. COMPARISON WITH ANTIMYCIN A AND POTASSIUM CYANIDE UNDER AEROBIC CONDITIONS.

Budzicka E, Niepokojczycka E, Szumiel I
Inst. Nuclear Res., 03-195 Warszawa, Poland
Neoplasma; 28(4):423-433 1981

Effects of treatment with misonidazole under aerobic conditions were examined in L5178Y-R and L5178Y-S cells. These cells slightly differ in susceptibility to the drug, however, the effects of treatment are similar: (1) slowing down growth without affecting viability at low doses; (2) cell lethality at higher doses with rapid elimination of dead cells from the population and resuming normal growth; (3) decrease in 3H-thymidine incorporation. These effects of misonidazole were strikingly similar to those of antimycin A (1 ug/ml) and KCN (1 mM). It seems that the common cause of the described manifestations of cellular damage inflicted by all three chemicals is energy depletion due to disturbances in the function of mitochondrial electron transport. (Author abstract) (29 Refs)

16. CHARACTERIZATION OF A VERY-LOW-DENSITY LIPOPROTEIN (VLDL)-ASSOCIATED CYTOTOXIC FACTOR.

Chan SY, Pollard M
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Br J Cancer; 44(3):410-417 1981

A VLDL-associated cytotoxic factor was isolated from sera of pregnant rats and characterized. The inhibitory effect of this factor on the macromolecular synthesis of rat prostate adenocarcinoma cells (PA-III) was also examined. VLDL (Sf 20-400) was subfractionated by differential ultracentrifugal flotation and the Sf 100-400 fraction was associated with most of the oncolytic activity. Chemical analysis of serum VLDL at various stages of pregnancy indicated that the four major constituents of VLDL at various stages of VLDL (protein, triglyceride, cholesterol, and phospholipid), and the cytotoxic titer, were increased significantly before parturition and restored to normal levels by 24 hr post partum. The delipidation of lyophilized VLDL by n-heptane suggested that the cytotoxic component was associated with the neutral lipid core of VLDL. Kinetic studies of colony inhibition and the incorporation of radioactive thymidine and leucine into 10% TCA precipitates of PA-III cells showed that VLDL induced irreparable cellular damage during the initial 15 hr of incubation. The cytotoxic activity of VLDL was not due to the association with PGF2alpha, beta-estradiol, progesterone, 25-hydroxycholesterol, or free fatty acids (oleic, stearic, palmitic, linoleic, linolenic and arachidonic acids), monopalmitolein, elaidyl and alpha-linolenyl alcohol. The role of this factor in host defense against neoplasia is discussed. (Author abstract) (36 Refs)

17. 1-BETA-D-ARABINOFURANOSYLCYTOSINE STIMULATES THYMIDINE INCORPORATION INTO THE DNA OF CONTACT-INHIBITED CELLS.

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Fairchild Center Biological Sciences, Columbia Univ., New York, NY, 10027
Exp Cell Res; 135(2):427-435 1981

In rapidly proliferating cells 1-beta-D-arabinofuranosylcytosine (ara-C) is a potent inhibitor of DNA synthesis whose effect can be irreversible and consequently cytocidal. Whereas thymidine incorporation is greatly reduced in rapidly proliferating cells in the presence of ara-C, contact-inhibited cells, similarly treated, show increased thymidine incorporation by as much as seven-fold This ara-C induced stimulation appears to result from an influence on thymidine utilization rather than increased DNA synthesis. (Author abstract) (20 Refs)

18. STUDIES ON THE MECHANISM OF CHLORAMBUCIL CYTOTOXICITY, I. ALTERATIONS OF METAL CONTENTS IN HUMAN TUMOR CELLS (MEETING ABSTRACT).

Moawad H, Barranco S, Ahmed AE
Departments of Pathology and Cell Biology, University of Texas Medical Branch, Galveston, TX
Toxicologist; 1(1):107 1981

The effects of lethal doses of chlorambucil, a widely used antitumor drug, on the transport of cations, having cellular and membranous physiological functions have been studied in cultured human tumor cells (AGS6) obtained from an adenocarcinoma of the stomach. A dose survival study revealed that 1, 6 and 15 ug/ml were equivalent to LD10, LD50 and LD90 respectively. A time course study showed that such lethal doses inhibited cell growth after 8 hr, 3 hr and 1 hr respectively. The intracellular and extracellular contents of sodium, potassium, calcium, zinc, magnesium, iron and copper ions were determined after each lethal dose at the indicated time intervals using atomic absorption spectrophotometry. Intracellular sodium, potassium, copper and magnesium were significantly reduced by 28-76%, 2-66%, 16-48% and 12-33% respectively. Meanwhile, intracellular calcium, zinc and iron were significantly elevated by 159-354%, 21 4-507% and 25-57% respectively. LD10 decreased sodium, potassium, magnesium, iron and copper by 5-67%. While potassium and iron were also decreased by LD50 and LD90, sodium, magnesium, and copper were increased in the membranous fraction. Calcium and zinc contents of such fractions were elevated at all doses. These data imply a toxic effect of chlorambucil on metal homeostasis. (no Refs)

19. TAMOXIFEN-INDUCED GENERALIZED LIPIDOSIS IN RATS SUBCHRONICALLY TREATED WITH HIGH DOSES.

Lullmann H, Lullmann-Rauch R
Dept. Pharmacology, Univ. Kiel, Kiel, W. Germany
Toxicol Appl Pharmacol; 61(1):138-146 1981

To determine whether the antiestrogenic and antineoplastic agent tamoxifen (TMX) induces generalized lipidosis, female Wistar rats were kept on a TMX-containing diet for 6-14 wk. The daily TMX doses ranged 100 to 130 mg/kg. Light and electron microscopic examination of liver, popliteal lymph nodes, adrenal glands, anterior pituitary gland, retina, nucleus supraopticus of the hypothalamus, and superior cervical ganglion showed increased numbers of intensely staining lamellated and crystalline-like cytoplasmic inclusions. Necrosis and gradual replacement by abnormal vacuolated cells were observed in the adrenal cortex. The degree of lipidosis depended upon the dose of TMX and duration of treatment. (15 Refs)

20. THE MOLECULAR BASIS FOR COMPLEXATION OF ADRIAMYCIN WITH FLAVIN MONONUCLEOTIDE AND FLAVIN ADENINE DINUCLEOTIDE.

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Dept. Pharmacology, Northwestern Univ. Medical Sch., Chicago, IL, 60611
Arch Biochem Biophys; 212(1):20-36 1981

A molecular level investigation of the interaction of anthracycline (ATC) antibiotics with flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) was conducted in view of the potential significance of such reactions in cardiotoxicity and drug metabolism and the ability of NADPH-cytochrome P-450 reductase to most effectively catalyze the reduction of adriamycin (ADM) with electron transfer via the FMN (or FAD) prosthetic group. The nature, strength, and specificity of ADM complex formation with FMN or FAD was studied. Results indicated that ADM can produce saturable, temperature- and concentration-dependent shifts of certain proton resonances of FMN and FAD to high field. The structures of FMN, FAD, and ADM in soln, as well as the mechanism of self-association, are requisite to the development of a molecular model for the ADM-FMN or the ADM-FAD complex. The most likely configuration assumed for the FMN-ADM complexation positions the planar rings of ADM over the aryl ring of FMN such that maximal ring current effect is experienced by the H-9 proton of FMN. A similar orientation is expected for the FAD-ADM complex. The formation of bimolecular complexes between the flavins and ADM, such that the ADM quinone moiety is positioned above the aromatic rings of isoalloxazine, appears to be consistent with the activity of flavoprotein reductases toward ADM. Cytochrome P-450 reductase exhibits a 30-fold greater activity towards ATC reductive glycosidic cleavage than the next most active reductase enzyme, xanthine oxidase, which contains only FAD as its prosthetic group. It was a suggested that a correlation may exist between the formation of molecular level complexes involving ATC antibiotics and FMN or FAD, the metabolic generation of ATC-free radicals, and reactive oxygen species and ATC-induced cardiotoxicity. (43 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

21. A STUDY OF FACTORS RELATED TO THE ACTION OF 1-PROPARGYL-5-CHLOROPYRIMIDIN-2-ONE (NY 3170) AND VINCRISTINE IN HUMAN MULTICELLULAR SPHEROIDS.

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Dept. Tissue Culture, Norsk Hydro's Inst. Cancer Res., Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Eur J Cancer Clin Oncol; 17(9):1053-1059 1981

Cells of the line NHIK 3025, originating from a human cervix carcinoma in situ, were protected against the lethal effects of the mitotic inhibitors 1-propargyl-5-chloropyrimidin-2-one (NY 3170) and vincristine when treated as multicellular spheroids in vitro. Cell survival was measured as retained colony-forming ability after 24 hr of treatments and the survival values of cells exposed in spheroids were 10-100x higher than the survival values obtained by parallel treatments of exponentially growing monolayer populations of the same cell line. By exposure of spheroids to radioactively labeled drugs and subsequent autoradiography, it was verified that both NY 3170 and vincristine were able to penetrate the cell mass in the spheroid. Monolayer populations in the plateau phase of growth were also resistant and this suggests that the resistance of spheroids to NY 3170 and vincristine may be associated with a subpopulation of resting cells. The metaphase-arresting properties of both drugs were expressed in the spheroids, as an accumulation of cells in metaphase was observed following drug treatment. (Author abstract) (24 Refs)

22. RESISTANCE AGAINST CIS-DICHLORODIAMMINEPLATINUM IN CULTURED CELLS WITH A HIGH CONTENT OF METALLOTHIONEIN.

Bakka A, Endresen L, Johnsen AB, Edminson PD, Rugstad HE
Dept. Surgery, Akershus Central Hosp., N1474 Nordbyhagen, Norway
Toxicol Appl Pharmacol; 61(2):215-226 1981

Resistance against the antitumor drug cis-dichlorodiammineplatinum (cis-DDP) was investigated in cultured cells with a high metallothionein (MT) content. Human epithelial cells (HE), mouse fibroblast cells (Cl 1D), and Cd-resistant substrains of both cell lines (HE100 and Cl 1D100, respectively) were tested. Spectrophotometry and amino acid analysis confirmed that cytoplasmic Cd-binding proteins in Cd-resistant strains were MT. After cis-DDP treatment (3-60 uM), sensitivity was tested by colony formation in soft agar or monolayer for Cl 1D and Cl 1D100 cells. All cell types were tested by interval counting over a 4-day growth period (0.5-60 uM cis-DDP). Results after 15 uM cis-DDP for 1 hr showed a 3.7% survival for C1 1D cells and 31.4% for C1 1D100 cells. Results of cell counts were dose-dependent: at 5 uM cis-DDP, values were 12.7% of control growth for C1 1D, 51.1% for C1 1D100, 8.4% for HE, and 31.7% for HE100. The results suggest correlation between high content of low mol wt Cd-binding proteins and resistance against cis-DDP. Possible mechanisms for development of resistance include increased DNA repair, cell location in 'tumor sanctuaries,' and increased synthesis of glutathione which can sequester toxic chemicals. (53 Refs)

23. INFLUENCE OF SOLE OR COMBINED TREATMENT WITH X-RAYS, QUINACRINE OR CHLOROQUINE ON GROWTH AND MELANIN FORMATION OF SERIALLY CULTURED MOUSE MELANOMA CELLS (HPM-73 LINE) (MEETING ABSTRACT).

Schachtschabel DO, Biller H, Leising HB
Institut fur Physiologische Chemie, Philipps-Universitat Marburg, D-3550 Marburg, W. Germany
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

Exposure of Harding-Passey melanoma cells (HPM-73) in monolayer culture during exponential growth phase to a single x-ray dose of 200 or 400 Rad resulted in retardation (up to 3 days) followed by resumption of cell proliferation. Eight hundred Rad (or higher doses) caused a significant reduction of survival rate. This growth-inhibitory effect was augmented by continuous incubation in the presence of quinacrine (atebrine) or chloroquine (resochine) at concentrations which alone were slightly or not inhibitory. Combinations of 800 Rad and 6 x 10-6M quinacrine or chloroquine resulted in death of all cells. The specific melanin content (E400/mg cell protein) of cultures treated (6 days) with quinacrine alone was not affected, while irradiation or exposure to chloroquine alone led to a moderate increase (up to 50%). A more pronounced elevation was reached by combined treatment with x-rays and quinacrine or chloroquine. The effects of quinacrine and chloroquine on x-ray irradiated cells might be related to their DNA repair inhibiting properties. (no Refs)

24. REVERSAL OF EFFECTS OF ALKYLATING AGENTS THROUGH THE USE OF PROSTAGLANDIN E1 IN THE OVOTESTIS OF THE SNAIL LYMNAEA ACUMINATA.

Singh R, Agrawal RA
Dept. Zoology, Univ. Gorakhpur, Gorakhpur 273 001, India
Curr Sci; 50(17):780-781 1981

Cyclophosphamide and busulfan induced significant reductions in DNA, RNA and protein concentrations in treated snails, Lymnea Acuminata. Administration of prostaglandin E1 eliminated these reductions. The use of prostaglandins for countering the toxic effects of alkylating agents used in chemotherapy is suggested. (8 Refs)

25. INHIBITION OF BLEOMYCIN-INDUCED DNA BREAKAGE BY SUPEROXIDE DISMUTASE.

Galvan L, Huang CH, Prestayko AW, Stout JT, Evans JE, Crooke ST
Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Res; 41(12):5103-5106 1981

Inhibition of bleomycin (BLM)-induced DNA breakage by superoxide dismutase (SOD) has been reported and presumed to be due to its removal of the superoxide free radicals generated by BLM in the presence of iron(II). We have studied the possibility that the inhibitory effect might result from DNA-binding of SOD. The effect of copper-zinc SOD on BLM-induced DNA degradation was investigated using the PM-2 DNA fluorescence technique. PM-2 DNA was incubated with BLM in the presence or absence of native and heat-inactivated copper-zinc SOD as determined by the epinephrine autoxidation method. The concentrations of SOD required to inhibit 50% PM-2 DNA degradation for the native and the inactivated SOD were 100 and 120 ug/ml, respectively. Analysis of the reaction mixture by agarose gel electrophoresis confirmed the absence of DNA degradation by BLM in the presence of either form of SOD. PM-2 DNA was shown to bind native or inactivated SOD by Sephadex G-100 column chromatography, fluorescence-quenching studies, and agarose gel electrophoresis. Thus, these results indicate that SOD is able to bind to PM-2 DNA and inhibit BLM-induced degradation independently of its free radical-scavenging activity. The inhibition was more effective against BLM than other compounds which degrade PM-2 DNA. This suggests that SOD may bind to BLM-binding and/or BLM degradation sites in PM-2 DNA, and the observed inhibition is unrelated to its effects on free radicals. (Author abstract) (19 Refs)

26. THE EFFECT OF THE CHEMOTHERAPEUTIC DRUG VM-26 AND HYPERTHERMIA ON THE SURVIVAL OF MAMMALIAN CELLS IN VITRO (MEETING ABSTRACT).

Kostic L, Djordjevic O, Brkic G, Arsenovic-Sobic V
Radiobiological Laboratory, Institute of Nuclear Sciences 'Boris Kidric', Beograd, Yugoslavia
Strahlentherapie; 157(9):619 1981

In this communication the interaction of chemotherapeutic agent and hyperthermia treatment is studied under the conditions which favored the suppression of repair processes. We have investigated the effect of one relatively new anticancer drug VM-26 (Sandoz) on the survival of mammalian cells in normal and hyperthermic conditions (42 C). NCTC clone 929 of L cells cultivated in Eagle's medium supplemented with 20% calf serum was used throughout in these investigations. L cells in logarithmic phase of growth were treated with different concentrations of VM-26(0.1-10 ug/ml of medium) for various time periods at 37 or 42 C. Immediately after the treatment cells were washed with Hanks' soln and fresh medium was adde d for further 10 days of incubation. Survival after treatment was found by assays using the colony-forming method. The results show that the survival after treatment at 37 C depends on drug concentration and exposure time of cells to the agent. Treatment of cells at elevated temperature either simultaneously, before or after hyperthermia results in potentiation of the killing effect induced by this drug. (no Refs)

27. CIS-ACONITYL SPACER BETWEEN DAUNOMYCIN AND MACROMOLECULAR CARRIERS: A MODEL OF PH-SENSITIVE LINKAGE RELEASING DRUG FROM A LYSOSOMOTROPIC CONJUGATE.

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Dept. Pathology and Pharmacology, Boston Univ. Sch. Medicine, Boston, MA, 02118
Biochem Biophys Res Commun; 102(3):1048-1054 1981

Conjugation of N-cis-aconityl daunomycin (ADM) and N-maleyl daunomycin (MDM) to aminoethyl polyacrylamide beads (Affi-Gel 701) and to poly(D-lysine) is described. Release of free daunomycin (DM) from ADM-Affi-Gel 701 in citrate-phosphate buffer was monitored by spectrophotometric absorption at 475 nanometers between pH 4 and 7. At pH 4, the half-life of hydrolysis was less than 3 hr; DM concentration in supernatant reached a max at 6 hr. DM was released from the cis-aconityl linkage at pH 5 and 6 with half-lives of 6 and 96 hr, respectively. At pH 7 the linkage was stable, with no detectable DM in the supernatant after 4 day. Max DM released at pH 4 was 50-66% of total DM bound to AFFi-Gel; thin-layer chromatography demonstrated that the released DM was unaltered. Growth inhibition of WEHI-5 mouse monocytic leukemia cells was greater than 90% if ADM-Affi-Gel (3 x 10(-7) M DM) was exposed to pH 5 buffer prior to addition to cell culture. Lack of cytotoxicity of the conjugate when incubated at pH 7 indicated stable cis-linkage at neutral pH even in the presence of cultured cells. ADM-poly(D-lysine) caused 90% inhibition of WEHI-5 cells at concentrations of 1 x 10(-7) M. Comparable addition of MDM-poly(D-lysine) conjugates was not inhibitory. Unlike the Affi-Gel conjugate, ADM-poly(D-lysine) appears to enter cells and reach the lysosomal compartment. The cis-aconityl spacer may release DM in the acidic milieu of lysosomes due to participation of a free cis-carboxylic group. (16 Refs)

28. INFLUENCE OF INDUCERS OF MONOOXYGENASES ON CYTOTOXIC EFFICIENCY OF ELLIPTICINE ON LEUKEMIA L1210 CELLS.

Lesca P, Monsarrat B, Cros S, Paoletti C
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, Centre National de la Recherche Scientifique, 205, Route de Narbonne, Toulouse Cedex 31078, France
JNCI; 67(4):871-876 1981

The effects of some inducers of microsomal cytochrome P450-dependent monooxygenases on the metabolic bioactivation and the cytotoxicity of the antitumoral drug ellipticine (ELPT) were studied. Rate of growth of leukemia L1210 cells was measured in vitro in the absence and presence of ELPT or measured when the ELPT was metabolically transformed by noninbred Sprague-Dawley rat liver microsomes. The animals used were either untreated or pretreated by various inducers such as phenobarbital, 3-methylcholanthrene, beta-naphthoflavone, 2,3,7,8-tetrachlorodibenzo-p-dioxin, Aroclor 1254, or ELPT. The transformation of ELPT into its two main metabolites, 9-hydroxyellipticine (9-OHE) and 7-hydroxyellipticine, was studied and measured by high-pressure liquid chromatography in conjunction with the determination of cytotoxic activity. A large variability was observed in the bioactivation and cytotoxic efficiency of ELPT mediated by the different microsomal preparations. The more P448 and/or P1-450 forms of cytochrome were induced, the more the 9-OHE was produced and the more the cytotoxicity toward L1210 cells was enhanced. These features were compared with those elicited by the activation of cyclophosphamide, which was transformed into cytotoxic metabolites by the cytochrome P450 form specifically induced by phenobarbital-type inducers. (Author abstract) (27 Refs)

29. EFFECT OF BETA ADRENERGIC AGONISTS AND BETA BLOCKING AGENTS ON HEMOPOIESIS IN HUMAN BONE MARROW.

Dresch C, Minc J, Poirier O, Bouvet D
Service de Medecine nucleaire, 2, place du Docteur-Fournier, 75474 Paris Cedex 10, France
Biomedicine; 34(4):93-98 1981

The effect of propanolol (nonspecific blocking agent), acebutol (beta1 blocking agent), butoxamine (beta2 blocking agent) and several beta adrenergic agonists was studied on 3H-thymidine (3H-TdR) incorporation and granulomonocyte colony formation in agar by human bone marrow. Only butoxamine and propanolol decreased 3H-TdR incorporation by total normal bone marrow cells at concentrations above 10(-6) M for butoxamine and 10(-5) M for propanolol. Autoradiography showed that inhibition of 3H-TdR incorporation by butoxamine was slightly more pronounced on neutrophil precursors than on red cell precursors (neutrophil series LI..53 and erythroblasts .67 compared to control bone marrow cells at 10(-5) M concentration). The development of granulo-monocyte colonies in agar culture was delayed by preincubation with butoxamine at concentrations above 5 x 10(-6) M. Hydroxyurea suicide showed that this was due to a decrease in the number of CFU-C in S phase. Beta2 blocking agents are able to decrease the number of normal hematopoietic cells entering S phase. This effect is seen on both neutrophil and erythroblastic precursors and on granulo-monocyte progenitors. It could be used as a means of protecting bone marrow cells during cancer intensive chemotherapy. (Author abstract) (18 Refs)

30. SELECTIVE KILLING OF TRANSFORMED CELLS IN COMBINATION WITH INHIBITORS OF POLYAMINE BIOSYNTHESIS AND S-PHASE SPECIFIC DRUGS.

Sunkara PS, Fowler SK, Nishioka K
Merrell Res. Center, Merrell Dow Pharmaceuticals Incorporated, 2110 E. Galbraith Rd., Cincinnati, OH, 45215
Cell Biol Int Rep; 5(10):991-997 1981

The effect of alpha-difluoromethyl ornithine (DFMO) on cell growth and cell cycle traverse was studied in normal WI-38 and 3T3 and transformed SV-WI-38 (2RA), SV-3T3, and HeLa cells. Cells were grown in the presence or absence of 2.5 milliM DFMO for 96 hr. DFMO inhibited polyamine synthesis, resulting in the disappearance of intracellular putrescine and reduction of spermidine and spermine levels in most of the cell lines tested. Cell growth was reduced 36-70%, depending on cell line. Normal cells were arrested in the G1 phase of the cell cycle; transformed cells were arrested in the S phase. Normal WI-38 and transformed SV-WI-38 cells were exposed to 2.5 milliM DFMO for 4 days followed by the S-phase-specific drug cytosine arabinoside (Ara-C: 50 ug/ml) for 16 hr. Transformed cells were killed by Ara-C, but normal cells, in the G1 phase, were protected from the toxic effects of Ara-C. Results suggest that inhibitors like DFMO could be used therapeutically in combination with cytotoxic drugs. (21 Refs)

31. THE ENHANCEMENT OF EFFECT OF CHEMOTHERAPEUTIC DRUGS BY RADIOSENSITISERS (MEETING ABSTRACT).

Martin WM, McNally NJ
Gray Laboratory of the Cancer Research Campaign, Mount Vernon, Hospital Northwood, Middlesex, England
Br J Cancer; 43(5):729 1981

Cells from sc tumors of the culture-adapted sarcoma, WHFIB, were found to exhibit repair of potentially lethal damage (PLD) after treatment by cyclophosphamide (CY). Misonidazole (MISO) given 1 hr prior to CY inhibited this PLD repair and caused potentiation of Cy cytotoxicity, which was more marked at 24 hr than 4 hr after CY injection. One mg/g MISO caused a dose-modifying factor (DMF) of 2.1 with this system. Comparable effects were also found using the regrowth-delay assay. Other 2-nitroimidazole radiosensitizers also potentiated the action of CY. MISO given 6 hr before CY, simulataneously, or even 2 hr after, caused significant potentiation of cytotoxicity, but MISO given 1 hr before CY produced the optimal effect. There was a linear relationship between sensitizer dose and the regrowth delay following combined treatment. With melphalan, 1 mg/g MISO caused a DMF of 2.5. Two mm WHFIB lung tumors did not exhibit repair of PLD after CY and also showed less potentiation of CY cytotoxicity by MISO than sc tumors. Normal-tissue effects have been encouraging: the CY-induced LD50/60 was altered by less than 10% by combination with 1 mg/g MISO; and 1 mg/g MISO caused no significant increase in leukopenia with therapeutic doses of CY. (no Refs)

32. MECHANISMS OF IN VIVO CYTOTOXICITY OF RADIOPROTECTIVE WR-2721 (MEETING ABSTRACT).

Gaugas JM
Cancer Research Campaign Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, England
Br J Radiol; 54(640):368 1981

WR 2721 [NH(2)(CH(2))3NH(CH(2))2SH2PO(3)] is known to protect normal rather than neoplastic tissue against radiation damage in vivo. When WR-2721 was added to cultured cells (Bri8) there was arrest of proliferation due to diverse mechanisms. WR 2721 was oxidized to the 'thiolaminoaldehyde' antiproliferogen by polyamine oxidase (PAO) in fetal-calf serum (FCS, 10% supplement in medium). Optimally, the 50% inhibitory dose (ID50) for cell arrest was 150 uM WR-2721 at 7.5 ug/cm3 of purified PAO, ie equivalent to use of 24% FCS in cultures. Prior addition of excess catalase to cultures with WR-2721 failed to reduce cytotoxicity, and thereby eliminated H2O2 byproduct as the antiproliferogen in the system. Addition of reduced, but not oxidized, biogenic glutathione, L-cysteine and DL-homocysteine (greater than 1.0 mM) partially prevented cytotoxicity due to thiolaminoaldehyde adduction with sulfhydryl compounds. Inactivation of PAO with Na semicarbazide (50 uM), aminoguanidine (150 uM) or 3-hydroxybenzyloxyamine, which themselves were not cytotoxic, completely prevented WR-2721 oxidation and raised the ID50 to 4.5 mM. Since PAO occurs in liver, this WR-2721 conversion and SH adduction should be of pharmacological interest. Combined administration of a PAO inhibitor drug (pyridoxal and/or flavin co-factor inactivation) together with WR-2721 might spare its radioprotective capability or decrease cytotoxicity to benefit tumor radiotherapy. (no Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

33. ACTIVE TRANSPORT OF 5-FLUOROURACIL AND ITS ENERGY COUPLING IN EHRLICH ASCITES TUMOR CELLS.

Yamamoto SI, Kawasaki T
Dept. Biochemistry, Hiroshima Univ. Sch. Medicine, Kasumi, Minami-ku, Hiroshima 734, Japan
J Biochem (Tokyo); 90(3):635-642 1981

Ehrlich cells accumulated 5-fluorouracil (FUra) and its metabolites in the acid-soluble pool to a level 5x that in the medium in the presence of glucose after 60 min of incubation at 37 C. FUra taken up in 10 min under the same conditions was almost wholly present as the non-metabolized form, and the intracellular level of non-metabolized form was 2 and 3x the extracellular concentration after 30 and 60 min of incubation, respectively. The uptake of FUra was dependent on temperature with an optimum at 42 C. The initial rate of FUra uptake showed saturation kinetics with a Km for FUra of 0.63 mM. Pyrimidine analogs inhibited FUra transport competitively, and sulfhydryl reagents also inhibited the transport. These results indicate that presence of a carrier system specific for FUra, which catalyzes an active transport of FUra into Ehrlich cells. Concentrative uptake of FUra in the presence of glucose was inhibited by glycolytic inhibitors, but not by the addition of mitochondrial electron transfer inhibitors and uncouplers. The uptake rate of FUra was found to be dependent on cellular ATP concentration in the presence and absence of extracellular Na+. A decrease in the uptake rate at lower intracellular ATP level was due to a decrease in the Vmax value for FUra and the half-max velocity for the uptake was observed at 2.4 mM ATP regardless of the presence of extracellular Na+. Although FUra was accumulated in the absence of extracellular Na+ in Ehrlich cells, the initial rate of FUra uptake was increased 1.3-fold in the presence of an Na+ gradient (out greater than in) due to an increase in Vmax for FUra and the half-max velocity for Na+-dependent uptake was observed at 21 mM extracellular Na+ concentration. These results suggest that active transport of FUra into Ehrlich cells may be directly coupled to intracellular ATP. (Author abstract) (52 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

34. ENHANCEMENT OF ANTITUMOR EFFECT BY MAGNETIC CONTROL OF A MICROENCAPSULATED ANTICANCER DRUG.

Kato T
Dept. Urology, Akita Univ., Sch. Medicine, Hondo, Akita 010, Japan
Gan To Kagaku Ryoho; 8(5):698-706 1981

Responding to the need for selective cancer chemotherapy, magnetically controlled chemotherapy was investigated. For this purpose, two types of ferromagnetic mitomycin C microcapsules were prepared: an outer type with mean particle size of 308 um containing mitomycin C as a core covered with ethylcellulose and ferrite particles, and an interior type with mean particle size of 250 um containing both mitomycin C and ferrite particles as a core covered with ethylcellulose. In vitro analysis of these capsules indicated their sustained-release property and sensitive magnetization. Animal studies showed that the capsules could be guided in the aorta under the usual magnetic filed exerted from a conventional magnet. V2 tumors in the rabbit limb and urinary bladder were successfully treated by magnetic control of the capsules in the artery and bladder, respectively. Pharmacokinetic studies revealed that the magnetically controlled chemotherapy markedly increased the prolonged drug absorption into the target tissues, thus enhancing the antitumor effect of the encapsulated drug. The results strongly suggest the feasibility and effectiveness of magnetic control of a microencapsulated anticancer drug in the artery and/or luminal spaces. The prospect of this kind of cancer treatment is discussed. (11 Refs) (In JPN)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

35. SYNTHESIS AND ANTIMETABOLIC ACTIVITY OF DL-THREO-3-FLUOROASPARTATE (FASP) AND DL-THREO-3-FLUOROASPARAGINE (FASN) (MEETING ABSTRACT).

Duschinsky R, Walker R, Wojnarowski W, Brunner KT

Swiss Insititute for Experimental Cancer Research, CH-1006 Epalinges, Switzerland

Experientia; 37(6):668 1981

FAsp and FAsn were synthesized by a new stereoselective chemical procedure which mimics in part the biological degradation of orotate. Growth of Escherichia coli 1345 in a minimal medium was 100% inhibited by 0.6 ug/ml FAsp. The action of graded FAsp doses was reversed exclusively by equimolar L-Asp doses. FAsn was 100 x less inhibitory. In cultures of L1210 and L5778Y cells containing 5 ug/ml Asn, FAsn caused dose-dependent growth inhibition. Twenty-five ug/ml caused lysis. In presence of 55 ug/ml Asn complete protection against the toxicity exerted by 10 ug/ml FAsn was achieved whereas 100 ug/ml FAsn caused lysis. Asp offered no protection and FAsp had only marginal antileukemia activity. (no Refs)

INTERFERON AND OTHER ANTIVIRALS

36. EFFECT OF 2'5'-OLIGOADENYLIC ACID ON A MOUSE CELL LINE PARTIALLY RESISTANT TO INTERFERON.

Panet A, Czarniecki CW, Falk H, Friedman RM

Dept. Virology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel

Virology; 114(2):567-572 1981

We have investigated the sensitivity of a mouse cell line, NIH 3T3 (clone 1), that was found to be resistant to the anticellular and certain antiviral activities of interferon, to 2',5'-oligoadenylate (2'5'A). The 2'5'A was introduced into the cells by coprecipitation with calcium phosphate and by increasing cell permeability with lysolecithin. In both cases neither cellular protein nor DNA synthesis was inhibited by 2'5'A in the NIH 3T3 cells. In contrast, the synthesis of proteins and DNA in L cells, an IFN sensitive line, was inhibited by low concentrations of 2'5'A. Furthermore, treatment of the infected cell cultures with 2'5'A resulted in the inhibition of vesicular stomatitis virus (VSV) replication in L cells but not in NIH 3T3 cells. The production of MuLV in NIH 3T3 cells was also not affected by 2'5'A. These observations, together with our previous finding that NIH 3T3 (clone 1) cells are deficient in RNase F activity suggest that activation of the RNase F by 2'5'A is responsible for the inhibition of both protein and DNA synthesis in sensitive cells. (Author abstract) (20 Refs)

37. SPECIFIC HIGH-AFFINITY BINDING OF 125I-LABELED MOUSE INTERFERON TO INTERFERON RESISTANT EMBRYONAL CARCINOMA CELLS IN VITRO.

Aguet M, Gresser I, Hovanessian AG, Bandu MT, Blanchard B, Blangy D

(c/o Gresser) Lab. Viral Oncology, Institut de Recherches Scientifiques sur le Cancer, BP 8, 94802 Villejuif, France

Virology; 114(2):585-588 1981

Multipotential mouse embryonal carcinoma cells are resistant to several biologic effects of mouse interferon: inhibition of viral multiplication and inhibition of cell division. Nevertheless using 125I-labeled highly purified mouse interferon we have shown that these embryonal carcinoma cells express specific interferon receptors in similar number and of the same affinity as interferon sensitive differentiated embryonal carcinoma cells. Thus, mechanisms of interferon resistance are probably multiple : some cells are resistant because they lack specific binding sites for interferon (interferon resistant mouse L1210 cells) and other cells, as shown herein, are resistant to some of the effects of interferon despite binding of interferon to specific receptor sites. Furthermore, these binding sites may be considered functional, since interferon does induce an increase in 2-5A synthetase in these cells. (Author abstract) (9 Refs)

38. INTERFERON INCREASES THE ABUNDANCE OF SUBMEMBRANOUS MICROFILAMENTS IN HELA-S3 CELLS IN SUSPENSION CULTURE.

Wang E, Pfeffer LM, Tamm I
Rockefeller Univ., New York, NY, 10021
Proc Natl Acad Sci USA; 78(10):6281-6285 1981

Human beta(fibroblast) interferon inhibits the proliferation of human HeLa-S3 carcinoma cells in suspension culture. Accompanying this effect, the lateral mobility of cell surface receptors for concanavalin A is decreased and the rigidity of the plasma membrane lipid bilayer is increased. The present findings show a marked increase in the number of polymerized actin-containing microfilaments 3 days after treatment of HeLa-S3 cells with beta-interferon (640 units/ml). The cortical region of the treated enlarged cells contains a thick and dense meshwork of 40-70 A microfilaments. The actin nature of the filaments was verified by their ability to bind heavy meromyosin. These results support the concept that beta-interferon induces a coordinated response in the plasma membrane and the underlying microfilaments in both tumor and normal cells. (Author abstract) (35 Refs)

39. INTERFERON INDUCTION IN PRIMATES BY STABILIZED POLYRIBOINOSINIC ACID-POLYRIBOCYTIDYLIC ACID: EFFECT OF COMPONENT SIZE.

Levy HB, Riley FL, Lvovsky E, Stephen EE
Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD, 20205
Infect Immun; 34(2):416-421 1981

Two series of interferon-inducing complexes containing polyriboinosinic and polyribocytidylic acids, poly-L-lysine, and carboxymethyl cellulose were prepared. One series contained carboxymethyl cellulose, 27,000-mol-wt poly-L-lysine, and either 4S, 6S, or 9S polyriboinosinic and polyribocytidylic acids. The other series contained carboxymethyl cellulose, 9S polyriboinosinic and polyribocytidylic acids, and poly-L-lysine, whose mol wt ranged from 2,000 to 27,000. The homogeneity of these double-stranded polynucleotide complexes was confirmed by single-step thermal denaturation profiles and by single peaks in sucrose gradient velocity sedimentation. The complexes have a greater resistance to hydrolysis by ribonuclease than does polyriboinosinic-polyribocytidylic acid. The resistance to ribonuclease increased with the increasing size of polynucleotide homopolymers and poly-L-lysine. In monkeys and, to a lesser extent, in mice, serum interferon levels induced by the different complexes were related to the degree of resistance of the complexes to hydrolysis by ribonuclease. In mice, 4S, 6S, and 9S complexes of polyriboinosinic-polyribocytidylic acid, poly-L-lysine, and carboxymethyl cellulose had a higher level of toxicity than did polyriboinosinic-polyribocytidylic acid as measured by 50% lethal dose. The toxicity was parallel to the ribonuclease resistance of the complexes. It was concluded that an increase in the size of the polynucleotides and the polyamino acids in these complexes leads to higher resistance to hydrolysis by ribonuclease and to greater interferon responses in mice and rhesus monkeys. (Author abstract) (8 Refs)

40. EFFECTS OF APHIDICOLIN ON RETROVIRUS DNA SYNTHESIS IN VIVO.

Hagino-Yamagishi K, Kano K, Mano Y
Dept. Physiological Chemistry and Nutrition, Univ. Tokyo, 7-3-1-Hongo, Bunkyo-ku, Tokyo, Japan
Biochem Biophys Res Commun; 102(4):1372-1378 1981

Aphidicolin (AC) markedly reduced progeny virus production in SC-1 cells newly infected with AKR-, Moloney-, and Friend-murine leukemia virus. The results of hybridization analysis of virus-specific RNA indicated that once viral DNA was integrated into the host cell genome, the transcription of viral DNA and progeny virus production were not inhibited by the drug, suggesting that the site of inhibition of AC exists in the process prior to the integration of viral DNA. The results of further experiments in which unintegrated viral DNA from AKR-virus-infected and uninfected SC-1 cells were analyzed by 1% agarose gel electrophoresis and by the Southern blotting technique indicated that DNA from infected cells with AC treatment lacked the large closed circular DNA, while the linear and the small closed circular DNA were still present; these experiments indicated that AC inhibition takes place during the formation of large closed circular DNA. The hybridization patterns of linear DNA fragments obtained by restriction endonuclease digestion were not altered by AC treatment of the cells. The same results were obtained by other restriction endonuclease digestions. Thus, AC apparently inhibits the conversion from linear DNA to large closed circular DNA. (14 Refs)

41. 2-L-RHAMNOPYRANOSYL[1,2,4]TRIAZOLO[1,5-A]PYRIDINE. 4' AND 3' OXIDATION PRODUCTS. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS.

Allard P, Dinh TH, Gouyette C, Igolen J, Chermann JC, Barre-Sinoussi F
Unite de Chimie Organique, Institut Pasteur, Equipe de Recherche Associee au CNRS (ERA 927), 75724 Paris, Cedex 15, France
J Med Chem; 24(11):1291-1297 1981

A series of 2-alpha-L-rhamnopyranosylnitro[1,2,4]triazolo[1,5 alpha]pyridine C-nucleosides was synthesized from the condensation of a thioiminoether with nitro-2-pyridylhydrazines. Catalytic reduction afforded the corresponding amino derivative. A 1',2' unsaturated C-nucleoside was also obtained by two different routes. Selective oxidation gave the 3'- and 4'-ketonucleosides. The cytotoxic properties of the nucleosides, as well as their effect on viral transformation and replication, were described. The nitro derivatives inhibit viral replication, but at toxic doses; the introduction of a keto function leads to a product which inhibits the replication of murine leukemia virus (MuLV) at noncytotoxic concentrations. The amino derivatives have no significant antiviral effect. (Author abstract) (26 Refs)

42. REPRESSION AND ACTIVATION OF THE GENOME OF HERPES SIMPLEX VIRUSES IN HUMAN CELLS.

Wigdahl BL, Isom HC, Rapp F
(c/o Rapp) Dept. Microbiology and Specialized Cancer Res. Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Proc Natl Acad Sci USA; 78(10):6522-6526 1981

We have described previously a cell culture system in which the herpes simplex virus (HSV) Type 2 (HSV-2) genome is maintained in a repressed form after treatment of infected cells with 1-beta-D-arabinofuranosylcytosine and increase of incubation temperature from 37 C to 39.5 C. Infectious HSV-2 production was activated by altering incubation temperature or by superinfecting with human cytomegalovirus. We now report the establishment of an analogous system utilizing HSV Type 1 (HSV-1). Human embryo lung cells were infected with HSV-1 and treated with 1-beta-D-arabinofuranosylcytosine (25 ug/ml) for 7 days to minimize both synthesis of virus DNA and infectious virus while allowing expression of early virus genes. HSV-1 was maintained in an undetectable form for at least 72 days when the incubation temperature was raised from 37 C to 40.5 C after removal of the inhibitor. HSV-1 gene expression was then predictably turned on by superinfection with human cytomegalovirus or by reducing the incubation temperature. Virus replicated after activation was compared with the respective parental virus with regard to inhibition by the HSV-1-specific antiviral (E)-5-(2-bromovinyl)-2'-deoxyuridine and EcoRI, HindIII, and Xba I restriction endonuclease cleavage patterns. The results show activation of HSV gene expression in human cells by a human cytomegalovirus early gene function(s), followed by synthesis of parental-like HSV. (Author abstract) (24 Refs)

OTHER RELATED STUDIES

43. MULTICELLULAR TUMOUR SPHEROIDS FROM HUMAN BRAIN TUMORS. A MODEL FOR EXPERIMENTAL CHEMOTHERAPY IN VITRO? (MEETING ABSTRACT).

Oktar N, Darling JL, Thomas DG
Department of Neurological Surgery, Institute of Neurology, Queen Square, London WC1N 3BG, England
Cell Biol Int Rep; 5(SupplA):42 1981

Multicellular tumor spheroids have been obtained from a range of fourteen primary and secondary human brain tumors. Tumor biopsies were minced, disaggregated with collagenase and the resultant cell suspension diluted to 5x10(5) cell/ml and inoculated into flasks coated with 0.5% agar. After approx one wk in static culture, single spheroids (mean vol 1.4 x 10(6) um(3)) were transferred into individual agar coated wells on a microtitration plate. At least 10 spheroids were used for each trial. They were exposed to graded concentrations of various chemotherapeutic agents (lomustine, Procarbazine, Vincristine, VM-26, Adriamycin, Mithramycin, L-asparaginase and Methotrexate) for 24 hr at 37 C. After treatment, drugs were removed, the spheroids washed and refed with fresh growth medium. The growth medium of treated and non-treated (control) spheroids was changed twice weekly throughout the assay. The spheroids were measured daily using an eye piece um for a 10 day period following drug removal and the growth delay calculated. Spheroids were also disaggregated after drug treatment and the colony forming efficiency in soft agar was determined. A dose dependant correlation was observed between both relative growth delay and cell survival with these cytotoxic agents. However, patterns of chemotherapeutic response were found to vary considerably between different tumor types and even between tumors of similar histopathology. The effects of corticosteroids, interferon and cyclic nucleotides on human tumor multicellular spheroids was also assessed using the same system. Spheroids produced from human brain tumors may be useful as models for the study of general biology as well as a model for experimental in vitro chemosensitivity. (no Refs)

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ANTITUMOR AND ANTIVIRAL AGENTS
Mechanisms of Action

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. INDUCTION OF DEOXYRIBONUCLEIC ACID DAMAGE IN HELA S3 CELLS BY CYTOTOXIC AND ANTITUMOR SESQUITERPENE LACTONES.

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Dept. Pharmaceutical Technology and Biochemistry, Technical Univ. Gdansk, 80-952 Gdansk, Poland

Biochem Pharmacol; 30(21):3005-3007 1981

Effects of parthenolide, 1,10-epoxyparthenolide, alatolide, eupatoriopicin, vern olepin, elphantopin, and costunolide on DNA synthesis and cellular growth were tested. Incubation of HeLa S3 cells with 202 uM parthenolide resulted in an almost complete inhibition of DNA synthesis in subcellular systems derived from the cells. Addition of the cytoplasmic fraction from untreated cells did not reverse inhibition, suggesting that interference with DNA templates plays a major role. All of the lactones induced DNA damage in HeLa cells at 35 and 75x their ED50 doses. The lactones did not cause DNA breaks in isolated DNA. Results supported the theory that alkylation of DNA is a molecular basis for biological activity of sesquiterpene lactones. (16 Refs)

2. THE COMPARATIVE EFFECTS OF 5-AZACYTIDINE AND DIHYDRO-5-AZACYTIDINE ON POLYSOMAL RNA IN EHRLICH ASCITES CELLS IN VITRO.

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Mol Pharmacol; 20(3):644-648 1981

To determine if differences in cytotoxicity between azacytidine (AZC) and dihydro-5-azacytidine (DHAZC) result from their effects on the posttranscriptional processing of nuclear (n) RNA or from modification of the translational activity of drug-substituted messenger (m) RNA, the synthesis of polysomal ribosomal (r) RNA, transfer (t) RNA, and mRNA [poly(A)RNA], and the translational activity of AZC- and DHAZC-modified poly(A)RNA were determined in Ehrlich ascites cells in vitro. A significant difference was observed in the potency of these drugs as exhibited by their relative inhibitory effects on the synthesis of rRNA in Ehrlich ascites cells in vitro. At 10(-5) M AZC, 28 S and 18 S rRNA synthesis was inhibited 65% and 35%, respectively, whereas 10(-4) AZC inhibited both 28 S and 18 S rRNA by 70%. In contrast, 50% inhibition of 28 S and 18 S rRNA was produced only at 10(-3) M DHAZC. The amount of cytidine analogue incorporated into a particular species of RNA was not proportional to its effect on the synthesis or function of that RNA. Although rRNA and 4 S RNA contained equivalent amounts of AZC, only the synthesis of rRNA was inhibited. Similarly, poly(A)RNA contained the highest specific radioactivity of labeled AZC and DHAZC. Results suggested that the primary site of action of AZC and DHAZC appears to be related to its inhibitory effect on rRNA. The relative differences in potency between AZC and DHAZC as antitumor agents correlates closely with their respective inhibitory effects on rRNA synthesis and their incorporation into this species in RNA. (30 Refs)

3. DETECTION OF DNA SINGLE-STRAND BREAKS PRODUCED DURING THE REPAIR OF DAMAGE BY DNA-PROTEIN CROSS-LINKING AGENTS.

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Cancer Res; 42(1):145-149 1982

In this investigation, the combination of 1-beta-D-arabinofuranosylcytosine and hydroxyurea was used to inhibit the polymerase step of DNA excision repair. The DNA single-strand breaks (SSB), which accumulated in the presence of these agents, were measured by alkaline elution. With this approach, DNA SSB were detected in normal human fibroblasts after exposure to trans-platinum(II)diamminedichloride, formaldehyde or potassium chromate. These agents all share the common feature in that they induce DNA-protein cross-links in mammalian cells. In the case of trans-platinum(II)diamminedichloride or formaldehyde, the frequency of these SSB was markedly less in excision-deficient xeroderma pigmentosum cells. With chromate, a high level of SSB was induced in both normal and xeroderma pigmentosum cells; these results indicate that chromate damage to DNA is repaired by a mechanism different than the classical excision pathway since xeroderma pigmentosum cells responded normally. Several other agents were investigated with this approach, and no SSB were detected with nickel sulfate, 12-O-tetradecanoylphorbol-13-acetate or asbestos fibers in the presence or absence of the polymerase inhibitor. This approach was found to be a very sensitive method to detect DNA excision repair. (Author abstract) (21 Refs)

4. RELATIONSHIP BETWEEN IN VIVO MITOMYCIN C EXPOSURE, SISTER CHROMATID EXCHANGE INDUCTION AND IN VITRO MITOGENIC PROLIFERATION. II. EFFECT OF AGING ON SPLEEN CELL MITOGENESIS AND SISTER CHROMATID EXCHANGE INDUCTION.

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Oncology Center, Johns Hopkins Univ. Medical Center, Room1-127, Baltimore, MD, 21205

Mech Ageing Dev; 17(2):203-209 1981

In vivo administration of mitomycin C (MMC) produces an increase in both the frequencies of sister chromatid exchange (SCE) as well as inhibition of in vitro mitogenic responses. At low concentrations of MMC (2 mg/kg) spleen cell suspensions from both young and old mice showed similar patterns of mitogen inhibition and increased SCE frequencies. At high MMC concentrations (5 mg/kg) significant differences between young and old responses were observed. Spleen cells from young animals displayed mitogen-inhibition curves which plateaued with increasing doses of MMC, while the cells from old animals displayed a continuing increase in mitogenic inhibition. MMC-induced SCE frequencies revealed a complementary pattern: increasing SCE frequencies as a function of MMC concentration in young spleen cells while SCE levels plateaued in old spleen cell populations. The results of these studies suggest (1) that an inverse relationship exists between sister chromatid exchange induction and mitogenic response, (2) that cells from older animals may have an increased sensitivity to high levels of DNA damage (5 mg/kg MMC), and (3) that this sensitivity may be expressed functionally by increased inhibition of in vitro mitogenic responses. (Author abstract) (18 Refs)

5. UNSTABLE AMPLIFICATION OF AN ALTERED DIHYDROFOLATE REDUCTASE GENE ASSOCIATED WITH DOUBLE-MINUTE CHROMOSOMES.

Haber DA, Schimke RT
Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305
Cell; 26(3,part1):355-362 1981

We have studied a line of 3T6 mouse fibroblasts grown in progressively increasing concentrations of methotrexate. Initially, drug resistance results from amplification of the gene encoding the normal dihydrofolate reductase. Growth of these methotrexate-resistant populations at higher methotrexate concentrations results in the emergence of cells expressing high levels of dihydrofolate reductase with a reduced methotrexate affinity. Using the fluorescence-activated cell sorter, we demonstrate that the variant gene is not present in the population of cells resistant to lower levels of methotrexate, and hence we postulate that the mutational event occurred in cells already containing multiple normal dihydrofolate reductase genes. Growth of the variant cells in the absence of selection is associated with the permanent loss of the altered genes and the disappearance of double-minute chromosomes, on which these genes reside. The pattern of accumulation and loss of double-minute chromosomes is reproduced following transformation of methotrexate-sensitive cells with the altered genes. Our results are consistent with autonomous replication of double-minute chromosomes and a selective advantage of cells with the smallest number of extrachromosomal elements necessary for survival at a given methotrexate concentration. (Author abstract) (26 Refs)

6. INHIBITION OF PURIFIED HUMAN AND HERPES SIMPLEX VIRUS-INDUCED DNA POLYMERASES BY 9-(2-HYDROXYETHOXYMETHYL)GUANINE TRIPHOSPHATE. EFFECTS ON PRIMER-TEMPLATE FUNCTION.

Derse D, Cheng YC, Furman PA, StClair MH, Elion GB
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J Biol Chem; 256(22):11447-11451 1981

The inhibition of highly purified herpes simplex virus (HSV)-induced and host cell DNA polymerases by the triphosphate form of 9-(2-hydroxyethoxymethyl)guanine (acyclovir; acycloguanosine) was examined. Acyclovir triphosphate (acyclo-GTP) competitively inhibited the incorporation of dGMP into DNA, catalyzed by HSV DNA polymerase; apparent Km and Ki values of dGTP and acyclo-GTP were 0.15 uM and 0.003 uM, respectively. HeLa DNA polymerase alpha was also competitively inhibited; Km and Ki values of dGTP and acyclo-GTP were 1.2 uM and 0.18 uM, respectively. In contrast, HeLa DNA polymerase beta was insensitive to the analogue. The 'limited' DNA synthesis observed when dGTP was omitted from HSV or alpha DNA polymerase reactions was inhibited by acyclo-GTP in a concentration-dependent manner. Prior incubation of activated DNA, acyclo-GTP, and DNA polymerase (alpha or HSV) resulted in a marked decreased in the utilization of the primer-template in subsequent DNA polymerase reactions. This decreased ability of preincubated primer-templates to support DNA synthesis was dependent on acyclo-GTP, enzyme concentration, and the time of prior incubation. Acyclo-GMP-terminated DNA was found to inhibit HSV DNA polymerase-catalyzed DNA synthesis. Kinetic experiments with variable concentrations of activated DNA and fixed concentrations of acyclo-GMP-terminated DNA polymerase revealed a noncompetitive inhibition of HSV-1 DNA polymerase. The apparent Km of 3'-hydroxyl termini was 1.1 x 10(-7) M, the Kii and Kis of acyclo-GMP termini in activated DNA were 8.8 x 10(-8) M and 2.1 x 10(-9) M, respectively. Finally, 14C-labeled acyclo-GMP residues incorporated into activated DNA by HSV-1 DNA polymerase could not be excised by the polymerase-associated 3',5'-exonuclease activity. (Author abstract) (15 Refs)

7. CYTOKINETIC AND BIOCHEMICAL EFFECTS OF 5-IMINODAUNORUBICIN IN HUMAN COLON CARCINOMA IN CULTURE.

Glazer RI, Hartman KD, Richardson CL
NCI, Building 37, Room 6D28, Bethesda, MD, 20205
Cancer Res; 42(1):117-121 1982

The semisynthetic anthracycline, 5-iminodaunorubicin (IM), was investigated to see whether modification of the benzoquinone moiety to produce a drug with low free radical potential would alter the cytotoxic and biochemical characteristics of this drug in comparison to Adriamycin (ADR), an agent with high free radical potential. Cell viability was measured in human colon carcinoma (HT-29) cells by soft-agar cloning. Upon exposure of either log-phase or early plateau-phase cells for 2 hr to IM or ADR, a threshold exponential cell lethality curve was obtained. Prolonging drug exposure to 24 hr produced an exponential decline in cell survival and a marked reduction in viability of both log-phase and early plateau-phase cells. Inhibition of DNA synthesis in log-phase cells after 2 and 24 hr of exposure to IM and ADR paralleled the increased cell lethality produced by the drugs. In contrast, total RNA synthesis was not inhibited by IM, whereas ADR impaired both RNA and DNA synthesis. Nuclear rRNA synthesis was not significantly inhibited following 24 hr of exposure to 10(-7) M ADR or IM but was inhibited by 85 and 35% at 10(-6) M ADR or IM, respectively. The affinity of IM and ADR for HT-29 DNA was measured in vitro by displacement of acridine orange binding and was found to be similar for both analogs. These studies suggest that the cytotoxicity of IM and ADR results from the interactions of these drugs with DNA. (Author abstract) (20 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

8. HORMONAL REGULATION OF ZINC METABOLISM IN A HUMAN PROSTATIC CARCINOMA CELL LINE (PC-3).

Giles PJ, Cousins RJ
(c/o Cousins) Dept. Food Science and Human Nutrition, Univ. Florida, Gainesville, FL, 32611
Cancer Res; 42(1):2-7 1982

Cells from a human prostatic adenocarcinoma cell line (PC-3) were maintained in M199 medium, with and without 5% baby calf serum, to examine aspects of cellular zinc metabolism. Cultures contained 0.5 to 1.0 x 10(6) cells/dish. Enhanced 65Zn accumulation in response to dexamethasone was observed after 24 hr in culture. the rate of efflux of accumulated 65Zn was not influenced by this hormone. Dihydrotestosterone had no effect on the accumulation of 65Zn by whole cells. Between 60 and 75% of the accumulated 65Zn was found in the cytosol (166,000 x g supernatant) fraction. Analysis of zinc distribution in cytosol by gel filtration chromatography revealed two major zinc-containing peaks, one comprised of high-mol-wt zinc-containing proteins and a low-mol-wt fraction that eluted identically to purified metallothionein (MT). Ion exchange chromatography of this low-mol-wt fraction resolved it into two components comparable to the major forms of MT purified from liver. Prior to differential 65Zn accumulation (12 hr), increased 65Zn was bound to the MT-like fraction in dexamethasone-treated cells and increased [35S]cystine was incorporated into this protein fraction. Other steroid hormones (dihydrotestosterone, hydrocortisone), as well as prostaglandin E2, resulted in an increased amount of bound 65Zn in the MT fraction, while estradiol and cortisone had no effect. Incubation of cells with actinomycin D or cycloheximide blocked the stimulatory effect of dexamethasone on the prostatic MT-like fraction. These experiments suggest that the MT genes are expressed in prostatic carcinoma cells. Moreover, they show that various aspects of prostatic zinc metabolism, particularly those related to MT, are influenced by certain steroid hormones, namely dexamethasone and dihydrotestosterone. (Author abstract) (33 Refs)

9. FREDERICAMYCIN A, A NEW ANTITUMOR ANTIBIOTIC. II. BIOLOGICAL PROPERTIES.

Warnick-Pickle DJ, Byrne KM, Pandey RC, White RJ
Chemotherapy Fermentation Program, Frederick Cancer Res. Center, Post Office Box B, Frederick, MD, 21701
J Antibiot (Tokyo); 34(11):1402-1407 1981

Fredericamycin A is a novel antibiotic produced by a soil isolate of Streptomyces griseus (FCRC-48). In vitro, fredericamycin A exhibits antibacterial, antifungal, and cytotoxic activities. In vivo, fredericamycin A exhibits very good antitumor activity against P388 mouse leukemia as well as the CD8F mammary tumor and marginal activity against B16 melanoma. Fredericamycin A failed to demonstrate any interaction with DNA and inhibited protein and RNA synthesis preferentially to DNA synthesis in Bacillus subtilis and P388 cells. (Author abstract) (11 Refs)

10. COMPARATIVE INHIBITION OF NUCLEAR RNA SYNTHESIS IN CULTURED MOUSE LEUKEMIA L1210 CELLS BY ADRIAMYCIN AND 4'-EPI-ADRIAMYCIN.

Wilson RG, Kalonaros V, King M, Lockwood R, McNeill M
Dept. Biochemistry, Coll. Medicine and Dentistry New Jersey, New Jersey Medical Sch., Newark, NJ, 07103
Chem Biol Interact; 37(3):351-363 1981

Adriamycin and 4'-epi-adriamycin were compared as to their effect on nRNA synthesis. 4'-Epi-adriamycin was a more effective inhibitor than the parent compound of RNA synthesis as measured by incorporation of [3H]uridine. Adriamycin inhibited all three species of nRNA (ribosomal, nonpoly(A)hnRNA, poly(A)hnRNA) to approx the same extent. 4'-Epi-adriamycin on the other hand inhibited the nRNA species in the following order: non-poly(A)hnRNA greater than ribosomal RNA greater than poly(A)hnRNA. The inhibitory effects of both drugs on incorporation of uridine into RNA were reversible at low concentrations (5 ug/ml). (Author abstract) (14 Refs)

11. COLCHICINE AFFECTS THE DISTRIBUTION OF ISOTOPE-LABELED H2O AND EXTRACELLULAR MARKERS IN RAT LIVER AND HEPATOMAS.

Lea MA
Dept. Biochemistry, New Jersey Medical Sch., Newark, NJ, 07103
Cancer Lett; 14(3):317-321 1981

Rats bearing Morris hepatoma 7777, Morris hepatoma 7288CTC, or LK1 colon tumor were treated with colchicine (175 or 250 ug/100 g body wt); reduced uptake of 3H2O into tumors was noted compared to animals not treated with colchicine. The distribution of [3H]methoxy-inulin and [14C]sucrose was inhibited by colchicine in hepatomas. (8 Refs)

12. TISSUE LACTATE LEVEL IN OXYTHIAMINE-TREATED TUMOR-BEARING ANIMALS AND PROPERTIES OF LACTATE DEHYDROGENASE.

Velichko MG, Petushok VG, Gorbach ZV, Trebukhina RV, Ostrovskii IuM
Dept. Metabolism Regulation, Acad. Sciences of Byelorussian SSR, Grodno, USSR
Vopr Med Khim; 27(5):594-600 1981

The effect of oxythiamine (OT: 12.5 mg/kg, daily, sc) on lactate metabolism was studied in random-bred albino rats bearing transplanted sarcoma 45. Twenty-two days after the tumors were transplanted, the rats were sacrificed and lactate levels in the liver, kidneys, blood, tumor tissue, and skeletal muscles were determined. Lactate levels in all tissues of the tumor-bearing animals were significantly lower than corresponding levels in tumor-free controls. The administration of the OT caused further decreases in lactate level. Correlation analysis of tumor lactate level or tumor wt with lactate level in other tissues showed that small tumors produced lactate while large tumors consumed lactate. The mechanism of the antitumor effect of OT was shown to be associated with its effect on the assimilation or redistribution of lactate (pyruvate) in tumor and other tissues. The OT administration caused normalization of isoenzyme spectrum of liver lactate dehydrogenase and changed the affinity of the enzyme for substrates. (36 Refs) (In RUS)

13. BIOCHEMICAL MECHANISM OF RESISTANCE OF CULTURED SARCOMA 180 CELLS TO 6-THIOGUANINE.

Lee SH, Sartorelli AC
(c/o Sartorelli) Dept. Pharmacology, Developmental Therapeutics Program, Comprehensive Cancer Center, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Biochem Pharmacol; 30(22):3109-3114 1981

A 6-thioguanine (6TG) resistant clone (S180/TG) of the murine neoplastic cell line Sarcoma 180 (S180) synthesized significantly less 6-thioguanosine 5'-monophosphate (6TGMP) than parent sensitive S180 cells when exposed to 6TG in culture. The decrease in the intracellular level of 6TGMP in S180/TG cells did not appear to be due to a change in the (a) rate of uptake of 6TG (or guanine), (b) synthesis and accumulation of 5-phosphoribosyl 1-pyrophosphate (PRPP) from glucose, (c) capacity to enzymatically convert 6TG (or guanine) to its corresponding 5'-mononucleotide in the presence of exogenous PRPP, or (d) rate of hydrolysis of phosphate groups from newly synthesized 6TGMP. Contrasting with the decreased conversion of 6TG to 6TGMP by S180/TG cells was the finding of significantly more guanine conversion to guanine nucleotides by intact S180/TG cells, a phenomenon that resulted in approx four- and two-fold greater incorporation of [8-14C]guanine into RNA and DNA, respectively, in resistant cells than in the parent sensitive subline. The findings suggest that the mechanism by which S180/TG cells achieve insensitivity to the 6-thiopurine was through decreased synthesis of analog nucleotide; this phenomenon appears to be the result of altered purine metabolism in resistant cells which selectively permits the conversion of guanine to guanine nucleotides, while suppressing the anabolism of 6TG to 6TGMP. (Author abstract) (17 Refs)

14. INHIBITORY EFFECTS OF FOUR ISOABRINS ON THE GROWTH OF SARCOMA 180 CELLS.

Lin JY, Lee TC, Tung TC
Dept. Biochemistry, Coll. Medicine, Natl. Taiwan Univ., Taiwan, Republic of China
Cancer Res; 42(1):276-279 1982

The four isoabrins were shown to be capable of inhibiting the growth of tumor cells in vivo when one-fifth of their median lethal dose was used. From the in vitro experiments, the doses required for 50% inhibition of protein biosynthesis are 3.2 pg, 45 ng, 32 ng, and 10 ng/ml for abrin-a, -b, -c, and -d, respectively. Except for abrin-b, a good correlation between the inhibitory effects of abrins on the tumor growth and protein biosynthesis was observed. These isoabrins show a moderate inhibitory effect of DNA biosynthesis. (Author abstract) (19 Refs)

15. LETHAL ACTIVITY AND KINETIC RESPONSE OF CULTURED HUMAN CELLS TO 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDINE.

Drewinko B, Yang LY, Barlogie B
Dept. Lab. Medicine, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(1):107-111 1982

Cytotoxic and cytokinetic effects of 4'-(9-acridinylamino)methanesulfon-m-anisidine (m-AMSA) were studied on a cultured human colon carcinoma and on a human lymphoma (T1) cell line. Proliferating cells were more susceptible (10-fold) to the cytotoxic effect of m-AMSA than were nonproliferating cells. The agent had minimal effects on DNA synthesis. A comparable exposure doses on m-AMSA, the degree of lethal cell damage exceeded inhibition of DNA synthesis by four-fold. Cells synchronized in different stages of the cell cycle were equally sensitive to the cytotoxic effects of the drug, although the major cytokinetic effect was a block in G2. A greater killing effect was obtained by fractionated delivery than by a comparable dose delivered at once. These results suggest that superior antitumor results may be achieved by adequately spaced low doses of m-AMSA in the treatment of sensitive human tumors. (Author abstract) (34 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

16. REDUCTION OF ADRIAMYCIN TOXICITY BY ASCORBATE IN MICE AND GUINEA PIGS.

Fujita K, Shinpo K, Yamada K, Sato T, Niimi H, Shamoto M, Nagatsu T, Takeuchi T, Umezawa H
Inst. Comprehensive Medical Science, Fujita-Gakuen Univ. Sch. Medicine, Toyoake, Aichi 470-11, Japan
Cancer Res; 42(1):309-316 1982

The effect of ascorbate in reducing Adriamycin toxicity has been examined in mice and guinea pigs. Ascorbate had no effect on the antitumor activity of Adriamycin in mice inoculated with leukemia L1210, but it significantly prolonged the life of mice and guinea pigs treated with Adriamycin. Adriamycin elevated lipid peroxide levels in serum and liver, and ascorbate prevented the elevation. The significant prevention of Adriamycin-induced cardiomyopathy by ascorbate was proved by means of electron microscopy. The earliest alterations of dilation of the sarcoplasmic reticulum and transverse tubular system and the appearance of a large number of cytoplasmic fat droplets, which were seen in cardiac tissue from guinea pigs receiving Adriamycin, were apparently reduced in animals that were treated with ascorbate. (Author abstract) (36 Refs)

17. EFFECTS OF NANDROLONE DECANOATE ON THE TOXICITY AND ANTI-TUMOUR ACTION OF CCNU AND FU IN MURINE TUMOURS.

Bibby MC, Double JA, Mughal MA
Clinical Oncology Unit, Univ. Bradford, Bradford BD7 1DP, England
Br J Cancer; 44(4):572-577 1981

Pre-treatment with the anabolic steroid nandrolone decanoate (ND) increases the LD50 of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and 5-fluorouracil (FU) in NMRI mice. Administration of ND did not affect the anti-tumor action of CCNU against a transplantable mouse adenocarcinoma of the colon (MAC 13) or the anti-tumor action of FU against MAC 26. In both tumor lines ND had no significant effect on tumor growth. These data suggest that an increase in the anti-tumor selectivity of these agents may be produced by pretreatment with ND. (Author abstract) (17 Refs)

18. SYNTHESIS OF AMINOALKYLTHIOPHOSPHORIC ACIDS.

Tong Z, Du Y
PLA Acad. Medical Sciences, Beijing, People's Republic of China
Yaoxue Xuebao; 16(4):302-305 1981

In recent yr, promising radiation-protective agents have appeared. The aminoalklythiophosphoric acids, especially S-2-(3-aminopropylamino)ethylthiophosphoric acid [WR-2721], can selectively protect normal tissue from radiation injuries while offering practically no protection for tumor tissues during radiotherapy. An improved method for the synthesis of aminoalkylthiophosphoric acids is described. Numerous aminoalkylthiophosphoric acids were prepared and screened for radiation-protective activities. (8 Refs) (In CHI)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

19. STUDIES ON THE MECHANISM OF DENATURATION OF CYTOCHROME P-450 BY CYCLOPHOSPHAMIDE AND ITS METABOLITES.

Gurtoo HL, Marinello AJ, Struck RF, Paul B, Dahms RP
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Biol Chem; 256(22):11691-11701 1981

In vivo depression of rat hepatic microsomal mixed function oxidase by cyclophosphamide, an important anti-cancer and immunosuppressive agent was investigated. Essentially exclusive metabolism-dependent binding to microsomal proteins of 14C from [4-14C]cyclophosphamide, compared with 3H from [chloroethyl-3H]cyclophosphamide, suggests the binding of the metabolite acrolein. Of the various metabolites and analogs of cyclophosphamide tested, only acrolein and 4-hydroxycyclophosphamide (which releases acrolein in soln) caused denaturation of microsomal cytochrome P-450 in vitro; this denaturation was identical with that produced by sulfhydryl reagents. Of the chemicals tested, only those containing either a free amino group (except lysine) and/or a free sulfhydryl group (eg semicarbazide, cysteine, glycine, glucosamine) effectively blocked (40-80%) the binding of 14C as well as protected against acrolein-induced denaturation of cytochrome P-450. These data further suggested interaction of cyclophosphamide metabolite with free amino and/or free sulfhydryl groups in proteins. However, comparison with [3H]aflatoxin B2a which interacts with free protein amino groups via the formation of Schiff bases, clearly attributed the preferential binding of 14c to cysteine sulfhydryl groups in these proteins. Studies on chemical models derived from reaction between acrolein and cysteine also supported this suggestion. When microsomes isolated from incubations metabolizing [4-14C]cyclophosphamide were subjected to gel electrophoresis, the major radioactive band detected by autoradiography was associated with a cytochrome P-450 band at 55,000 daltons, the major band induced by phenobarbital in the rat. These results strongly point to the possibility that a crolein is the cyclophosphamide metabolite responsible for the depression of the mixed function oxidase activities. Acrolein most likely produces this effect by alkylation of the sulfhydryl group(s) in the active site of cytochrome P-450. (Author abstract) (59 Refs)

20. ALTERATION OF GALLIUM-67 DISTRIBUTION IN TUMOR-BEARING MICE FOLLOWING TREATMENT WITH METHOTREXATE: CONCISE COMMUNICATION.

Chilton HM, Witcofski RL, Watson NE, Heise CM
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J Nucl Med; 22(12):1064-1068 1981

The effect of methotrexate (MTX) treatment upon Ga-67 distribution was investigated. Tumor bearing mice were injected with Ga-67 citrate at varying time intervals following MTX treatment administered either as a single dose or in multiple doses. Altered Ga-67 distribution was observed following MTX therapy, the general pattern showing decreased levels in blood and increased uptake in bone. MTX therapy decreased Ga-67 uptake in liver, tumor, and muscle. The effects of MTX are related to the dose and time interval between the administrations of MTX and Ga-67. The serum of MTX-treated mice had lower unsaturated iron binding capacities and higher levels of unbound Ga-67. Serum iron and iron binding in rats determined 20 hr after MTX therapy showed significantly higher levels of serum iron and lower levels of Ga-67 in blood, and the percent transferrin saturation was approximately 95%. These observations suggest that MTX inhibition of erythropoiesis elevates serum iron levels and decreases the availability of gallium-binding sites in serum, resulting in altered Ga-67 tissue distribution. (Author abstract) (19 Refs)

21. EFFECTS OF TUNICAMYCIN ON ANTHRACYCLINE RESISTANCE IN P388 MURINE LEUKEMIA CELLS.

Chou TH, Kessel D
(c/o Kessel) Dept. Oncology, Wayne State Univ. Sch. Medicine, 3990 John R., Detroit, MI, 48201
Biochem Pharmacol; 30(22):3134-3136 1981

The inhibition of glycoprotein synthesis in an adriamycin (ADR)-resistant subline of P388 murine leukemia (P388/ADR) was studied for its effects on anthracycline responsiveness and drug efflux. Labeled daunorubicin (DR), cross resistant with P388/ADR in vivo, was used. Cell surface effects of tunicamycin (TC) were independently monitored by a two-phase partitioning method. TC inhibited fucose incorporation indicative of glycoprotein synthesis by 60%. TC increased the partition coefficient of both P388 and P388/ADR cells before and after neuraminidase treatment. Partitioning behavior was primarily affected by degree of membrane sialation, not by TC binding to cell surface. TC did not affect the capacity of P388 an P388/ADR cells for concentrative uptake of cycloleucine, non-metabolized amino acid. P388 and P388/ADR viabilit was decreased by approx 50% following 1 hr exposure to 0.0 ug/ml and 0.060 ug/ml DR, respectively. TC (3 ug/ml) inhibited P388 and P388/ADR cell growth for 24 hr; after that tim normal growth resumed. Exposure of TC-treated cells to DR had no effect on these results. Impaired DR accumulation, correctable by the addition of 10 milliM azide and deletion of glucose from the medium, was observed in P388/ADR cells. DR accumulation or efflux was not affected by prior exposure o either cell line to TC. Suppression of glycoprotein synthesis altered cell surface properties but had no effect on DR transpor characteristics or drug responsiveness. Enhanced glycosylation of cell surface components was associated with development o drug resistance patterns in P388/ADR, but was not a determinant of such resistance. (25 Refs)

22. THE METABOLISM OF CYCLOPHOSPHAMIDE BY ISOLATED RAT HEPATOCYTES.

Bates DJ, Foster AB, Jarman M
(c/o Jarman) Block F, Inst. Cancer Res., Clifton Ave., Sutton, Surrey, England
Biochem Pharmacol; 30(22):3055-3063 1981

The metabolism of cyclophosphamide was studied in vitro using isolated rat hepatocytes and mass spectrometry. The major product of primary oxidative metabolism in hepatocytes from phenobarbital treated rats was 4-hydroxycyclophosphamide, isolated as the O-ethyl derivatives, but dechloroethylation was also a substantial pathway. 4-hydroxycyclophosphamide was converted mainly into carboxyphosphamide and the formation of 4-ketocyclophosphamide was a minor pathway. Evidence is presented that under certain conditions a substantial amount of O-glucuronide of 4-hydroxycyclophosphamide was formed. The pattern of metabolism in hepatocytes otherwise resembled qualitatively that observed previously in vitro using subcellular fractions and in vivo, but quantitative differences were found. The metabolism of cyclophosphamide by hepatocytes resembles more closely that in vivo than does the metabolism in subcellular fractions, and hepatocytes should be the preferred in vitro system for studying the metabolism of anti-tumor agents. (Author abstract) (51 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

23. NEW DIMERIC ANALOGUES OF ETHIDIUM: SYNTHESIS, INTERACTION WITH DNA, AND ANTITUMOR ACTIVITY.

Kuhlmann KF, Mosher CW
Bio-Organic Chemistry Lab., SRI International, Menlo Park, CA, 94025
J Med Chem; 24(11):1333-1337 1981

Three new dimeric analogues of ethidium cation in which the monomeric moieties are linked at the 3' positions by alpha,omega-diethers of varying length and composition have been synthesized. The circular dichroism spectra of all three compounds indicate that they double intercalate, and their effects on the thermal helix-coil transition profile of poly(dA-dT) show extremely high affinity for helical DNA, with details of the binding interaction depending on the length and composition of the connectin g chain. The ability of the compounds to inhibit nucleic acid synthesis in L1210 cell culture also differed significantly, as did their antitumor effects against P388 leukemia and B16 melanoma. Compound 2, with 10 methylene groups in the connecting chain, is 5-20 x as potent as ethidium against murine P388 leukemia. These results clearly illustrate the advantage gained by incorporating a weak antitumor agent in a double-intercalating analogue. (Author abstract) (22 Refs)

24. SYNTHESIS AND EVALUATION OF GUANAZOLE PRODRUGS AS ANTINEOPLASTIC AGENTS.

Dias Selassie C, Lien EJ, Khwaja TA
Section Biomedicinal Chemistry, Univ. Southern California, Los Angeles, CA, 90033
J Pharm Sci; 70(11):1281-1283 1981

Nine amide derivatives of guanazole were synthesized, and eight of them were tested for antineoplastic activity versus L1210 cells in vitro. Several of these compounds exhibited activity comparable to or greater than that of guanazole. (Author abstract) (8 Refs)

25. ANTITUMOR ACTIVITY OF 3-NITROSO-2-OXAZOLIDONES.

Miyahara M, Miyahara M, Kamiya S, Maekawa A
Natl. Inst. Hygienic Sciences, 1-18-1 Kamiyoga, Setagaya, Tokyo, 158, Japan
Chem Pharm Bull (Tokyo); 29(8):2366-2369 1981

Antitumor activity of 2-oxazolidones in cyclic carbamate form and of their N-nitroso derivatives was tested. Some 3-nitroso-2-oxazolidones were active against rat ascites hepatoma AH13 and mouse lymphoid leukemia L1210; their alkylating activities were involved in the antitumor mechanism. 2-Oxazolidones were all inactive against AH13 and L1210; the compounds were not toxic to Donryu rats and CDF1 mice at the max dose tested (250-500 mg/kg in rats and 400 mg/kg in mice). Some 3-nitroso-2-oxazolidones were active against AH13 and/or L1210. Ethyl N-ethyl-N-nitrosocarbamate, 1-ethyl-1-nitrosourea, and the cyclic nitrosourea 1-nitrosourea-2-imidazolidone were tested for antitumor activities against both tumors. The cyclic nitroso compounds appeared to have a stronger antitumor effect and to be more toxic than corresponding acyclic nitroso compounds. Reactions of the nitroso and non-nitroso compounds were compared by a method using the 4-(p-nitrobenzyl) pyridine reagent. The non-nitroso compounds did not give any color reaction, but the nitroso compounds gave a purple color. The results suggest that the nitroso compounds are alkylating agents. No correlation was found between antitumor activity and color intensity. (11 Refs)

26. A COMPARISON OF THE INHIBITION OF BOVINE AND MURINE LEUKEMIA DIHYDROFOLATE REDUCTASE BY 4,6-DIAMINO-1,2-DIHYDRO-2, 2-DIMETHYL-1-(3-X-PHENYL)-S-TRIAZINES.

Guo ZR, Dietrich SW, Hansch C, Dolnick BJ, Bertino JR
(c/o Hansch) Dept. Chemistry, Pomona Coll., Claremont, CA, 91711
Mol Pharmacol; 20(3):649-656 1981

The inhibition of dihydrofolate reductase (DHFR) from bovine liver and murine (L 5178YR-C3) leukemia by 4,6 diamino-1,2-dihydro-2, 2-dimethyl-1-(3-X-phenyl)-s-triazines was studied to determine if significant differences exist between DHFR of healthy and tumor tissue. Congeners of the type 3-CH20-C6H4-Y were synthesized and tested to establish the role of Y in the inhibition of both DHFR. It is assumed that Y does not appear to contact DHFR hydrophobically or otherwise and hence has little effect on binding of congeners to the enzyme. Structure-activity relationships were studied. The triazines were more active at pH 7.20 than at pH 6.25, although little variation in structure-activity relationships were observed. The inhibition of bovine and murine DHFR by the congeners was compared. It was suggested that only 2-X substituents extending beyond the hydrophobic pocket of 1.6 defined by pi0 produce significant differences in the interaction with the two enzymes. The differences between the responses of the two enzymes were not large, but significantly beyond experimental error. Differences in response are discussed in term of Ki. Small differences in free energy resulting from minor variations in the conformation of the enzymes or hydrogen bonding ability may result in large differences in Ki. The implications of the possibility of differences between normal and tumor DHFR for the development of chemotherapeutic agents is discussed. (13 Refs)

27. ACTIVATED BLEOMYCIN: A TRANSIENT COMPLEX OF DRUG, IRON, AND OXYGEN THAT DEGRADES DNA.

Burger RM, Peisach J, Horwitz SB
Dept. Molecular Pharmacology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
J Biol Chem; 256(22):11636-11644 1981

Activated bleomycin is an oxygenated iron drug complex which embodies the drug's DNA-cleaving activity. This activity is exercised on DNA, if present, but if DNA is absent, the drug itself is inactivated. Hyperfine interactions in the EPR spectra of activated bleomycin prepared with 57Fe(II) and H2O2 demonstrate the presence of iron as Fe(III) and of bound oxygen originating in dioxygen. Bleomycin can also be activated with Fe(III) and either H2O2 or ethyl hydroperoxide. These latter reactions do not produce a ferrous intermediate nor do they require O2. But O2 is required for the reaction of activated bleomycin with DNA to yield the malondialdehyde-like chromogens used to monitor DNA degradation. The attack on DNA is quantitatively concurrent with the delay of activated bleomycin, however generated. (Author abstract) (39 Refs)

28. ELECTRON PARAMAGNETIC RESONANCE CHARACTERIZATION AND CONFORMATION OF DAUNORUBICIN SEMIQUINONE INTERMEDIATE IMPLICATED IN ANTHRACYCLINE METABOLISM, CARDIOTOXICITY, AND ANTICANCER ACTION.

Lown JW, Chen HH
Dept. Chemistry, Univ. Alberta, Edmonton, Alta., T6G 2G2, Canada
Can J Chem; 59(22):3212-3217 1981

The antitumor antibiotic daunorubicin, upon reduction in aqueous solution, gives a transient resolved epr spectrum of line width 17.0 G and g value of 2.0024. This is ascribed to the semiquinone previously tentatively assigned in the unresolved epr spectrum obtained by microsomal activation of the antibiotic. By reference to the epr spectrum of quinizarin semiquinone in aqueous solution the individual proton hyperfine splitting constants in both spectra were tentatively assigned by computer simulation. LCAO-MO calculations of one-electron wave function spin densities in both species gave good agreement between calculated and observed hfs for values of the parameters betaco/betacc = 1.8, deltaalpha = 1.4, allowing definite assignment of the aromatic protons. By considering the angular dependence of the ring A benzylic proton hfs it was possible to discriminate between two alternative half-chair conformations of daunorubicin semiquinone. The preferred conformation of the intermediate is tentatively assigned as that which places both 7 and 9 oxygen functions equatorial and the C-9 acetyl group axial. (Author abstract) (35 Refs)

EFFECTS OF ANTIMETASTATIC AGENTS

29. ANTICOAGULANTS AND EXPERIMENTAL METASTASES: EVALUATION OF ANTIMETASTATIC EFFECTS IN DIFFERENT MODEL SYSTEMS.

Maat B, Hilgard P
Radiobiological Inst., TNO, Rijswijk, Brugstraat 10, 5042 SB-Tilburg, The Netherlands
J Cancer Res Clin Oncol; 101(3):275-283 1981

The ability of the anticoagulants ancrod (AN), heparin (HP), and phenprocoumon (PPC) to produce antimetastatic effects in iv tumor systems (Lewis lung (3LL) carcinoma and B16 melanoma) and to reduce spontaneous metastases was studied. After iv injection of tumor cells into C57BL/Rij mice, a significant decrease in the number of lung colonies was found in mice pretreated with AN as compared to control animals. Continued AC did not decrease the number of lung metastases as compared to controls in either system. The mean blood coagulation times of 11 AC-treated animals were 10.4 min. Continued HP treatment was similarly unable to diminish the numbers of metastases in C57BL/Rij mice bearing sc transplanted tumors. The number of metastases was equal in HP-treated and control groups of both tumor systems. The size of the respective lung colonies or metastases did not differ significantly in the various experimental groups as compared to controls. In addition, the amputated tumor-bearing leg of the HP group did not differ significantly from the corresponding control group. The The number of spontaneous metastases in the PPC-treated animals was significantly reduced in both tumor systems as compared to untreated control animals. The results suggested that the capacity of circulating malignant cells to form spontaneous metastases is not influenced by most drugs having strong anticoagulant properties. Coumarin derivatives seem to have strong antimetastatic capabilities. (44 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

30. METHOTREXATE ANALOGUES. 14. SYNTHESIS OF NEW GAMMA-SUBSTITUTED DERIVATIVES AS DIHYDROFOLATE REDUCTASE INHIBITORS AND POTENTIAL ANTICANCER AGENTS.

Rosowsky A, Forsch R, Uren J, Wick M
Dept. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
J Med Chem; 24(12):1450-1455 1981

The gamma-tert-butyl ester, gamma-hydrazide, gamma-n-butylamide and gamma-benzylamide derivatives of methotrexate (MTX) were synthesized from 4-amino-4-deoxy-N(10)-methylpteroic acid (APA) and the appropriate blocked L-glutamic acid precursors with the aid of the peptide bond forming reagent diethyl phosphorocyanidate. The affinity of these side chain modified products for dihydrofolate reductase from Lactobacillus casei and L1210 mouse leukemic cells was determined spectrophotometrically or by competitive radioligand bindi assay, and their cytotoxicity was evaluated against L1210 le kemic cells in culture. The results provide continuing suppo for the view that the 'gamma-terminal region' of the MTX sic chain is an attractive site for molecular modification of this a ticancer agent. (Author abstract) (28 Refs)

31. 5-FLUORO- AND 5-CHLOROCYCLOPHOSPHAMIDE: SYNTHESIS, METABOLISM, AND ANTITUMOR ACTIVITY OF THE CIS AND TRANS ISOMERS.

Foster AB, Jarman M, Kinas RW, Van Maanen JM, Taylor G Gaston JL, Parkin A, Richardson AC
Mass Spectrometry-Drug Metabolism Group, Div. Chemistry, Ins Cancer Res., London, SW3 6JB, England
J Med Chem; 24(12):1399-1403 1981

In seeking analogues of cyclophosphamide (1) having im proved antitumor activity by virtue of accelerated formation c the cytotoxic metabolite phosphoramide mustard, cis and tran isomers of 5-fluoro- and 5-chlorocyclophosphamide (9,10,1 and 12, respectively) were synthesized by condensation of th appropriate 3-amino-2-halopropan-1-ol (13 or 26) with N,N bis(2-chloroethyl)phosphoramidic dichloride (14). The metabo lism of the halocyclophosphamides by rat liver microsome was stereoselective; the cis isomers (9 and 11) were poorly me tabolized, whereas the trans isomers (10 and 12) were metabo lized with efficiency comparable to that of cyclophosphamid However, there was no evidence that the yield of phosphora mide mustard produced by the trans analogues was significant ly greater than that from cyclophosphamide following micro somal 4-hydroxylation. Hence, the halogen substituents did no accelerate Beta-elimination of acrolein from the acyclic alde hydo tautomers. As expected, the poorly metabolized cis-5-flu oride (9) had little activity against the ADJ/PC6 tumor i mice. However, the cis-5-chloride (11) was as active as th trans isomer (12) and each had approximately half the thera peutic index of 1. The trans-5-fluoride (10) was much les active, having an ED90 value some 16-fold that of 1. (Autho abstract) (22 Refs)

32. ANTITUMOR ACTIVITY OF 5-HYDROXYMETHYL-2-FUROIC ACID.

Munekata M, Tamura G
Res. and Development Lab., Sapporo Breweries Ltd., Mita, Meguro ku, 153, Tokyo, Japan
Agric Biol Chem; 45(9):2149-2150 1981

The compound 5-Hydroxymethyl-2-furoic acid (65-I) ha been isolated from the ethylacetate extract of the culture broth and mycelium of Pyricularia grisea IAM 5051. The com pound was shown to have selective cytotoxicity against Simia virus 40 (SV40)-transformed cells in vitro and antitumor activi ty against Sarcoma 180 in vivo. The isolation procedure an physical characteristics of 65-I are described. The compoun had selective toxicity against SV40-transformed C3H-2K cell from day 1 at concentrations from 125 to 2,000 ug/ml; th minimum cytotoxic concentration increased with treatmen time. The total packed cell vol (TPCV) method was used t assay antitumor activity in vivo. Ascitic tumor cells of sarcom 180 were implanted ip in ICR mice (5 wk old, 17.5-20 g) Saline soln of the samples was administered 1x/day for 5 con secutive days (50 mg/kg x 5). The vol of tumor cells in ascite was measured on day 7. The ratio of TPCV of the test grou to that of the control group was 36.6; antitumor activity wa judged effective. (2 Refs)

33. USE OF AN HFR STRAIN OF E. COLI FOR PRESCREENING OF ANTITUMOR ANTIBIOTICS.

Tanida S, Hasegawa T, Yoneda M
Microbiological Res. Lab., Central Res. Div., Takeda Chemical Industries, 17-85, Juso-honmachi 2-chome, Yodogawa-ku, Osaka 532, Japan
Agric Biol Chem; 45(9):2013-2018 1981

An assay system with the Escherichia coli strain Hfr was examined for its ability to detect new antibiotics interacting with DNA. The screening system was established by the paper disc method at 42 and 32 C, using TE 120 and TE 144. Thirty antibiotics and five chemicals were tested. Some of the agents showed preferential activity against TE 120 at 42 C; however, some agents known to bind to DNA strands showed no activity. Nocardia sp. No C-14919 (N-1001) produced active metabolites which were new aminobenzoquinoid antibiotics, named dnacins. Dnacins showed preferential activity against the Hfr strain at high temperature in an aqueous condition. Dnacins A1 at 0.1 ug/ml and B1 at 0.05 ug/ml suppressed the growth of TE 120 at 42 C; twice the amount of each component did not markedly affect growth of TE 144 at 42 C. Thus, dnacins might show preferential activity against the replication machinery of F-like plasmids at effective concentrations. Dnacin B1 and dnacin A1 (0.05-0.1 ug/ml) caused a high frequency of plasmid loss from R 100-1 or F' gal-bearing strains without affecting growth of the host cells. The findings demonstrate that agents which interact with DNA are efficiently detected by the assay system. The relative ina ctivity of certain antibiotics may be explained by the permeability barrier of the test strain. (13 Refs)

34. FREDERICAMYCIN A, A NEW ANTITUMOR ANTIBIOTIC. I. PRODUCTION, ISOLATION AND PHYSICOCHEMICAL PROPERTIES.

Pandey RC, Toussaint MW, Stroshane RM, Kalita CC, Aszalos AA, Garretson AL, Wei TT, Byrne KM, Geoghegan RF, White RJ
Chemotherapy Fermentation Program, Frederick Cancer Res. Center, Post Office Box B, Frederick, MD, 21701
J Antibiot (Tokyo); 34(11):1389-1401 1981

A new antitumor antibiotic, fredericamycin A (FCRC-A48, NSC-305263), has been isolated from a strain of Streptomyces griseus (FCRC-48). Based on its unique UV-visible spectrum, infrared spectrum, proton and carbon-13 nuclear magnetic resonance spectra and mass spectra, it is judged to be a novel acid-base indicator type of compound. Its production, isolation and physicochemical properties are discussed. The isolation, UV-visible spectrum and some biological properties of two minor components, fredericamycin B and fredericamycin C, are also described. (Author abstract) (10 Refs)

35. ANTITUMOR AGENTS. 49. TRICIN, KAEMPFEROL-3-O-BETA-D-GLUCOPYRANOSIDE AND (+)-NORTRACHELOGENIN, ANTILEUKEMIC PRINCIPLES FROM WIKSTROEMIA INDICA.

Lee KH, Tagahara K, Suzuki H, Wu RY, Haruna M, Hall IH, Huang HC, Ito K, Iida T, Lai JS
Dept. Medicinal Chemistry, Sch. Pharmacy, Univ. North Carolina, Chapel Hill, NC, 27514
J Nat Prod; 44(5):530-535 1981

Active principles of Wikstroemia indica (Thymelaeaceae) were isolated by column chromatography of the active final chloroform extract on silica gel. Isolation led to the characterization of tricin, kaempferol-3-O-beta-D-glucopyranoside and (+)-nortrachelogenin as the major antileukemic constituents. Daphnoretin was identified as the potent antitumor principle against Ehrlich ascites carcinoma growth in mice. (21 Refs)

36. REDUCTION AND HYDROLYSIS OF 2-HYDROXYACLACINOMYCIN A.

Matsuzawa Y, Oki T
Central Res. Labs., Sanraku-Ocean Co., Ltd., 4-9-1 Johnan, Fujisawa 251, Japan
J Antibiot (Tokyo); 34(11):1495-1497 1981

Physicochemical and spectral properties of four 2-hydroxyaclacinomycin derivatives (M, N, S, and T) derived from the reduction and hydrolysis of 2-hydroxyaclacinomycin A are described. M and N (trisaccharide derivatives) showed marked cytotoxicity against cultured leukemia L1210 cells and preferentially inhibited RNA synthesis. S and T (di- and monosaccharide derivatives) were less active. (6 Refs)

37. TRISARUBICINOL, NEW ANTITUMOR ANTHRACYCLINE ANTIBIOTIC.

Yoshimoto A, Matsuzawa Y, Matsushita Y, Oki T, Takeuchi T, Umezawa H
Central Res. Lab., Sanraku-Ocean Co., Ltd., 4-9-1 Johnan, Fujisawa 251, Japan
J Antibiot (Tokyo); 34(11):1492-1494 1981

The microbial glycosidation of carminomycinone and 13-dihydrocarminomycinone by the mutant Streptomyces galilaeus strain KE303 yielded trisarubicinol. Characterization of trisarubicinol included elucidation of physicochemical properties, paramagnetic resonance spectrum, and antitumor activity against leukemia L1210 in CDF1 mice. (6 Refs)

INTERFERON AND OTHER ANTIVIRALS

38. INHIBITION OF CELLULAR AND VIRUS-ASSOCIATED NUCLEOTIDE POLYMERASES BY, AND ANTI-HERPES SIMPLEX VIRUS ACTIVITY OF, STREPTOVARICIN DERIVATIVES.

Srivastava BI, DiCioccio RA, Chadha KC, Rinehart KL
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263
Antimicrob Agents Chemother; 20(5):653-659 1981

Fourteen streptovaricin derivatives were tested for inhibition of cellular nucleotide polymerases (DNA polymerase alpha, DNA polymerase beta, and DNA polymerase gamma, terminal deoxynucleotidyltransferase [TdT], and RNA polymerase II), simian sarcoma virus deoxyribonucleic acid polymerase, and herpes simplex virus Type 1-induced deoxyribonucleic acid polymerase (HSV-DP). Three compounds (streptovadienal C, prestreptovarone, and streptoval Fc) preferentially inhibited TdT and HSV-DP over the other enzymes. These compounds inhibited HSV-DP more potently than they inhibited TdT. Evidence indicated that the mode of inhibition of TdT and HSV-DP by streptovadienal C and prestreptovarone was by interaction with the enzymes and not with template-primer, initiator, substrates, or divalent cations required for enzyme activity. Furthermore, data suggested that these compounds bind with greater affinity to HSV-DP than to TdT. Streptovadienal C and prestreptovarone were examined for their effect on the replication of herpes simplex virus Type 1 in African green monkey kidney (CV1) cells. These compounds produced 2-and 3-log drops in virus titer, respectively, at concentrations not significantly affecting cell viability. This correlated with evidence indicating a greater binding affinity of these compounds

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for HSV-DP over cellular nucleotide polymerases. (Author abstract) (27 Refs)

39. DIFFERENTIAL INHIBITION OF HERPES SIMPLEX VIRUSES, TYPE 1 (HSV-1) AND TYPE 2 (HSV-2), BY (E)-5-(2-X-VINYL)-2'-DEOXYURIDINES.

de Clercq E, Verhelst G, Descamps J, Bergstrom DE
Rega Inst. Medical Res., Minderbroedersstraat 10, B-3000 Leuven, Belgium
Acta Microbiol Acad Sci Hung; 28(3):307-312 1981

Antiviral activities of six (E)-5-(2-X-vinyl)-2'-deoxyuridines were tested in primary rabbit kidney cell cultures infected with laboratory strains of herpes simplex virus types 1 and 2. Four of the compounds may be useful as marker tests for rapid and specific diagnosis of human HSV-1 and HSV-2 infections. The tests may be less time-, labor- and reagent-consuming than many previously described typing techniques, including restriction endonuclease mapping. (15 Refs)

40. INTERFERON-MEDIATED DEPRESSION OF CYTOCHROME P-450-DEPENDENT DRUG BIOTRANSFORMAT ION.

Singh G, Renton KW
(c/o Renton) Dept. Pharmacology, Dalhousie Univ., Sir Charles Tupper Medical Building, Halifax, Nova Scotia B3H 4H7, Canada
Mol Pharmacol; 20(3):681-684 1981

The relationship between depression of hepatic cytochrome P-450 by Newcastle disease virus (NDV) and circulating interferon (IF) levels was studied in inbred strains of C3H/HeJ and C57BL/6J mice carrying the high (IF-1h) and low (IF-1l) production allele at the IF-1 locus. Twenty-four hr after the administration of NDV to C57BL/6J mice carrying the IF-1H allele, the mean circulating level of IF was 2,443 PRD50 units (amount of IF required for 50% plaque reduction). At the same time, cytochrome P-450 levels and aminopyrine N-demethylase (APDM) levels were depressed by 35% and 48%, respectively, in hepatic microsomes. In C3H/HeJ mice carrying the IF-1l allele, the circulating levels of IF were below the lowest limit of detection 24 hr after NDV treatment. In these mice, NDV had no effect of cytochrome P-450 or APDM activity levels. Twenty-four hr after the administration of poly(rI-rC), which induces IF formation via loci other than IF-1, high concentrations of IF were observed in the sera of both strains of mice. In C57BL/6J mice, cytochrome P-450 and and APDM activities were decreased by 44% and 50%, respectively, 24 hr after poly(rI-rC). In C3H/HeJ mice, cytochrome P-450 and APDM activities were decreased by 33% and 38% following poly(rI-rC) administration. In both strains, cytochrome b5 was unchanged following poly(rI-rC) treatment. It was concluded that an impairment of P-450-mediated drug biotransformation occurs via an IF-mediated interaction and that this effect may enhance the toxicity of drugs and exogenously administered chemicals. (20 Refs)

41. DIFFERENTIAL EFFECT OF IMIDAZOLE ANTIBIOTICS ON UNTRANSFORMED AND VIRUS-TRANSFORMED RAT CELL LINES.

Kuwano M, Akiyamu S, Kaneko M, Ikezaki K, Takaki R, Kimura G
Dept. Biochemistry and Internal Medicine, Oita Medical Sch., Hazama-cho, Oita 879-56, Japan
Cancer Res; 42(1):280-284 1982

The imidazole antimycotics clotrimazole and miconazole were tested on untransformed rat cell line 3Y1-B clone 1-6 (3Y1) and six transformed cell lines, which were independently isolated from 3Y1 or 3Y1-B clone 1 after infection with adenovirus 12 (AD-12) or with SV40, to determine their sensitivities to these drugs. The relative plating efficiency of three cell lines (T3, W4, and W5) transformed with AD-12 was reduced to 10(-1) of the initial value by clotrimazole (2 to 4 ug/ml), whereas that of the parental cell line 3Y1 was reduced to 10(-1) of the initial value by clotrimazole (20 to 25 ug/ml). By contrast, the differential effect of miconazole on 3Y1 and AD-12-transformed cell lines was found to be a factor of 2. The sensitivity of the SV40-transformed cell lines to these drugs was between the untransformed 3Y1 and the AD-12-transformed cell lines. The cellular sensitivity of untransformed 3Y1 cells to clotrimazole was significantly enhanced when exposed to various doses of the unsaturated fatty acid, linoleic acid. The untransformed and transformed cell lines showed sensitivities similar to the cytocidal activity of sterol-binding antimycotics, amphotericin B, and filipin. (Author abstract) (30 Refs)

42. EFFECT OF 1,4-DIHYDROXY-5,8-BIS (2-(2-HYDROXYETHYLAMINO)ETHYL AMINO)-9,10-ANTHRACENEDIONE (DIHYDROXYANTHRAQUINONE) ON THE REPLICATION OF SIMIAN VIRUS 40 CHROMOSOME.

Su RT
Dept. Microbiology, Univ. Kansas, Lawrence, KS, 66045
Biochem Biophys Res Commun; 103(1):249-255 1981

Dihydroxyanthraquinone (DHAQ) is an aminoanthraquinone derivative with potential anticancer activity. While SV40 infection of both permissive and nonpermissive cells stimulates cellular DNA synthesis, the presence of 1.6 nanoM DHAQ inhibited by approx 50% both cellular and viral DNA synthesis. Nearly 90% inhibition was observed at DHAQ concentrations of 0.4 uM or higher. Both RNA and protein synthesis was inhibited 50% in the presence of 0.8-8 uM DHAQ, where DNA synthesis is inhibited by 90%. Results indicate that both cellular and viral chromosome replication are inhibited to the same extent in cells treated with low concentrations of DHAQ. No detectable change in sedimentation on sucrose gradients was observed in viral chromosomes isolated either from DHAQ-treated cells or incubated directly with DHAQ at 2-10 uM. Aggregation of viral chromosomes occurred when very high DHAQ concentrations were used (greater than 20 uM). (21 Refs)

OTHER RELATED STUDIES

43. BROMOCRIPTINE: PRESENT AND FUTURE CONSIDERATIONS.

Guay AT
Section Endocrinology and Metabolism, Lahey Clinic, Boston, MA
Lahey Clin Found Bull; 30(1):24-27 1981

The actions, indications, results, mode of administration, adverse reactions, and potential uses of bromocriptine (BR) are discussed. BR shows the most promise among all drugs tested in recent yr for the effective medical treatment of pituitary tumors which cause acromegaly. (5 Refs)

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ANTITUMOR AND ANTIVIRAL AGENTS

Mechanisms of Action

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HE 20. 3173/2:

EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. NUCLEOLAR SILVER STAINED GRANULES IN RAT YOSHIDA SARCOMA CELLS AFTER RNA SYNTHESIS INHIBITION.

Kacerovska H, Likovsky Z, Smetana K
(c/o Smetana) Inst. Experimental Medicine, Czechoslovak Acad. Sciences, 128 00 Praha 2, Albertov 4, Czechoslovakia
Neoplasma; 28(5):513-516 1981

The number of nucleolar silver stained granules representing nucleolus organizer regions in interphase nuclei was studied in Yoshida ascitic sarcoma cells without and after the inhibition of the nucleolar RNA synthesis with actinomycin D or cyclophosphamide. The results demonstrated that the number of nucleolar silver stained granules decreased after the inhibition of the nucleolar RNA synthesis with these drugs disregarding the mode of their action. In addition, the decrease of nucleolar silver stained granules in number produced by actinomycin D was dose dependent. Similarly, the number of nucleoli without silver stained granules increased depending on the dose of the administered actinomycin D. (Author abstract) (13 Refs)

2. EFFECT OF N-BUTYRATE ON CELL CYCLE PROGRESSION AND IN SITU CHROMATIN STRUCTURE OF L1210 CELLS.

Darzynkiewicz Z, Traganos F, Xue SB, Melamed MR
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Exp Cell Res; 136(2):279-293 1981

In the presence of 1-5 mM n-butyrate, murine leukemic L1210 cells cease proliferation and become arrested in the G1A compartment of the G1 phase. Cells in this compartment are characterized by low RNA content and more condensed chromatin. During unperturbed growth the cell residence times in G1A are of indeterminate duration. The effect of n-butyrate in arresting cells in G1A was concentration-dependent. However, the sensitivity of L1210 cells to this drug was markedly enhanced when cells were treated for longer than one generation (12 hr). Cells arrested in G1A remained viable and when n-butyrate was removed, after a lag period, they resumed progression through the cycle. The effect of n-butyrate on cell progression through various parts of the cycle was studied in a stathmokinetic experiment. DNA in situ in nuclei of n-butyrate-treated cells had lowered (by 2-8 C) stability to thermal denaturation and increased (by 15%) accessibility to DNase I. DNA in situ in the nuclei of n-butyrate-treated cells also showed decreased sensitivity to acid-induced denaturation. Changes in chromatin were seen in all cells, regardless of cell cycle phase, within the first hr after addition of n-butyrate. Mitotic cells, however, reacted to n-butyrate more rapidly than interphase cells. The observed changes in L1210 cells are most likely a consequence of histone modifications (acetylation of inner histones, dephosphorylation of histone H1) induced by n-butyrate. (41 Refs)

3. SPECIAL SYMPOSIUM ON DERMATOLOGICAL THERAPY: III. PSORIASIS AND MYCOSIS FUNGOIDES. RAZOXANE.

Atherton DJ
Dept. Dermatology, Guy's Hosp., London SE1 9RT, England
Clin Exp Dermatol; 6(6):647-650 1981

Use of razoxane in the treatment of psoriasis and mycosis fungoides has been examined. Razoxane, a cytostatic bis-dioxopiperazine, arrests cell cycle progression only during premitotic (G2) and early mitotic (M) phases of the cell cycle. The drug inhibits a wide range of tumors, is well tolerated, and is not hepatotoxic. Treatment results in normalization of tumor microvasculature, which is likely responsible for the antimetastatic activity. For these reasons razoxane has also been useful in treatment of psoriasis. (12 Refs)

4. AN ANTIFOLATE-INDUCED LESION IN NEWLY SYNTHESIZED DNA.

Sedwick WD, Laszlo J
Dept. Medicine, Duke Medical Center, Durham, NC, 27710
Adv Enzyme Regul; 19:295-308 1981

Antifolates cause cells to accumulate exogenous UdR as dUMP in drug-treated cells. This accumulation of intracellular dUMP has no effect on inhibition of UdR incorporation into DNA. On the other hand, dUMP accumulation does result in detectable dUTP being synthesized and utilized as substrate for DNA synthesis. Although in the presence of metoprine (DDMP), dUMP is incorporated into DNA instead of TMP, the natural product of UdR substrate in the absence of the drug, DNA synthesis is equally rate limited by exogenous UdR. However, when analyzed on alkaline sucrose gradients, DNA which has incorporated exogenous UdR in the presence of antifolate sediments at 4S or less. This newly synthesized DNA accumulates preferentially while either synthesis of larger DNA is blocked, or high mol wt DNA is preferentially broken down as a result of DNA repair. These observations further increase the metabolic complexity of pathways that must be considered as underlying the differential toxicity of antifolates. (Author abstract) (32 Refs)

5. THE ROLE OF CYTOPLASMIC MICROTUBULES IN THE REGULATION OF THE ACTIVITY OF PEPTIDE GROWTH FACTORS.

Friedkin M, Rozengurt E
Dept. Biology, Univ. California, San Diego, La Jolla, CA, 92093
Adv Enzyme Regul; 19:39-59 1981

The enhancement of DNA stimulation by peptide growth factors in colchicine-treated cultures of Swiss 3T3 mouse fibroblasts appears to be associated with disassembly of cytoplasmic microtubules. Other antitubulin agents (colcemid, vinblastine, podophyllotoxin, nocodazole, and maytansine) also potentiate the effects of growth promoting factors such as insulin and EGF. The cytoplasmic microtubules are disrupted by antitubulin agents at concentrations very similar to those required for depolymerization of mitotic spindle microtubules. In the presence of highly radioactive [3H]thymidine, DNA synthesis can be stimulated in quiescent mouse fibroblasts without completion of the cell cycle. This makes possible studies of the potentiating effects of colchicine during the prereplicative period of the cycle uncomplicated by effects of the antitubulin agent on the mitotic spindle. The enhancing effects of colchicine can be demonstrated with sparse cultures of 3T3 fibroblasts as well as with 3T6 cells. Maytansine and colchicine need not be present during the initial period of interaction of peptides with the cell to produce enhancement of DNA synthesis. The enhancement can be obtained after transient exposure of cells to fetal bovine serum. The potentiating effects of antitubulin agents such as nocodazole, podophyllotoxin, and maytansine can be easily reversed whereas the enhancement with colchicine persists despite washing of cells. The stimulatory effects of insulin and EGF persist in cultures treated with antitubulin agents. The findings support the premise that after internalization the receptor-mitogen complex may remain active within endocytic vesicles when cells are exposed to colchicine. (Author abstract) (71 Refs)

6. INTERACTION OF THE ANTITUMOUR DRUG 4'-(9-ACRIDINYLAMINO)-METHANESULFON-M-ANISIDINE.HCL (M-AMSA) WITH NUCLEIC ACIDS.

Hudecz F, Kajtar J, Szekerke M
Res. Group for Peptide Chemistry, Inst. Organic Chemistry, L.Eotvos Univ., Budapest, H-1088, Hungary
Nucleic Acids Res; 9(24):6959-6973 1981

The interaction of AMSA with nucleic acids was studied by several techniques. Melting temperature and CD studies equally suggest that AMSA-binding is interfering with the secondary structure of DNA. An overlap by two mechanisms of binding seems to exist. Based on the CD measurements at low drug concentration intercalation is the most likely way of binding. At higher drug concentration stacking interaction predominates leading to cooperativity and formation of oriented sheets of aromatic ring-systems as reflected in the optical activity induced in the metachromatic band of the achiral drug. No base-pair specificity could be confirmed; however, a high affinity of AMSA to poly(A) chains was demonstrated. The CD measurements did not indicate any significant interaction with RNA. The selectivity of the AMSA-DNA interaction can be regarded as an important argument in favor of the role of this interaction in the antitumor effect of the drug. (Author abstract) (20 Refs)

7. THE ROLE OF FORMALDEHYDE IN METHYLENE DIMETHANESULPHONATE-INDUCED DNA CROSS-LINKS AND ITS RELEVANCE TO CYTOTOXICITY.

Bedford P, Fox BW
(c/o Fox) Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester, M20 9BX, England
Chem Biol Interact; 38(1):119-126 1981

The interaction of the antitumor dialkanesulfonate ester, methylene dimethanesulfonate (MDMS) with the DNA of Yoshida sarcoma cells has been studied using the technique of alkaline elution. A marked retention which was reversed by proteolytic treatment indicated the presence of DNA-protein cross-links. A small proteinase-resistant retention was also observed which indicated that a low level of DNA-DNA interstrand cross-links also occurred. Treatment of cells with the amounts of formaldehyde expected by hydrolysis of the drug showed proteinase-reversible DNA-protein cross-linking which on proteolytic removal revealed a small number of single-strand breaks. Thus, MDMS causes both DNA-protein and DNA-DNA interstrand cross-links, the former component being attributed totally to the formaldehyde produced on the drug's hydrolysis. Cell survival data showed formaldehyde to be comparatively non-cytotoxic, providing evidence that DNA-DNA cross-links observable by this technique may be associated with the cytotoxicity of MDMS. (Author abstract) (18 Refs)

8. EFFECTS OF THIOTEPA ON PRIMARY CULTURES OF DMBA-INDUCED MAMMARY TUMOURS OF RATS: KINETICS AND ULTRASTRUCTURE.

Fink SM, Tseng MT
Dept. Anatomy, Univ. Louisville, Louisville, KY, 40292
Br J Cancer; 44(5):762-765 1981

Effects of thiotepa (TP) on growth kinetics, thymidine labeling index (LI), and fine structure of cells cultured from mammary tumors induced by 7,12-dimethylbenz(alpha)anthracene (DMBA) in female Sprague-Dawley rats were determined. Cell subpopulations of these tumors were separated by isopycnic centrifugation. Primary cell cultures were obtained from band 3. Of the three parameters measured, the most obvious TP (10(-2) 10(-6) M)-induced changes were in the rate of DNA synthesis as determined by LI. At 10(-2) M TP, none of the remaining attached cells incorporated (3H)thymidine during pulse labeling. While the percentage of cells in S phase closely approximated the percentage of attached cells after treatment with 10(-6) M TP, the LI curve declined more sharply than the dose-response curves. Ultrastructural analysis revealed no viable cells remaining after 10(-2) M TP. At the lowest TP concentration (10(-6) M), the cells could not be distinguished from controls on the basis of fine structure. Cell-kinetic data indicated that growth inhibition of the selected DMBA-induced tumor cell subpopulation in culture by TP is dose-dependent. A good correlation was found between cell kinetics and labeling index. Indirectly, the study supports the concept of cell heterogeneity in solid tumors. (9 Refs)

9. ANTIPROLIFERATIVE ACTIVITY OF PROTOCATECHUALDEHYDE ON CHINESE HAMSTER CELLS GROWN IN CULTURE.

Nishimura M, Umeda M, Kusanagi A, Urakabe R, Yukimatsu K, Otawara S
Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, 2-33, Urafunecho, Minami-ku, Yokohama 232, Japan
Gan; 72(6):868-879 1981

The mode of cytotoxic action of protocatechualdehyde on V79 cells was examined. The cytotoxicity of protocatechualdehyde on V79 cells was time- and cell cycle-dependent. The lethal action is selective for the cells at S phase only. The cells lethally damaged at S phase seemed to complete their DNA synthesis, although the rate of DNA synthesis became lower and the duration of S phase was prolonged. Some cells arriving at G2 phase directly entered the next S phase without cell division and died of karyorrhexis or karyolysis. Cells treated at stages of the cell cycle other than S showed normal progression of their cell cycle to the G1/S boundary. The block point of the cell cycle seemed to lie a little behind that with hydroxyurea. When the cells at phases other than S were blocked with protocatechualdehyde for 14 hr, elongation of the next S phase occurred after removal of protocatechualdehyde. On alkaline sucrose gradient analysis, little scission of parental DNA was observed in the cells treated with protocatechualdehyde. (Author abstract) (12 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

10. ADRIAMYCIN-INDUCED CHANGES IN THE SURFACE MEMBRANE OF SARCOMA 180 ASCITES CELLS.

Murphree SA, Tritton TR, Sm[illegible] PL, Sartorelli AC
Dept. Pharmacology and Developmental Therapeutics Program, Comprehensive Cancer Center, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Biochim Biophys Acta; 649(2):317-324 1981

Adriamycin increases (a) the rate of agglutination of Sarcoma 180 cells by concanavalin A after brief exposure of 2-3 hr and (b) membrane fluidity as measured by ESR within 30 min of exposure at concentrations of the anthracycline at 10(-7)-10(-5) M. The effect of adriamycin on agglutination is not due to an increase in the number of surface receptors for concanavalin A, since the extent of binding of the lectin is not altered by adriamycin and no change occurs in the rate of occupancy of the concanavalin A binding sites by the lectin in cells treated with the antibiotic. The order parameter, a measurement of membrane fluidity, decreases in cells exposed to adriamycin and is dose-related. The results indicate that adriamycin can induce changes in the surface membrane of Sarcoma 180 cells within a brief period of exposure to a low but cytotoxic level of this agent. (Author abstract) (39 Refs)

11. SPECIFIC INHIBITION OF THE SUBUNITS OF RIBONUCLEOTIDE REDUCTASE AS A NEW APPROACH TO COMBINATION CHEMOTHERAPY.

Cory JG, Sato A, Lasater L

Dept. Biochemistry, Univ. South Florida Coll. Medicine, Tampa, FL, 33612

Adv Enzyme Regul; 19:139-150 1981

The activity of ribonucleotide reductase can be inhibited by agents such as hydroxyurea, guanazole, IMPY, MAIQ, IQ, Inox, 5'-deoxyinox and various deoxyribonucleoside triphosphates. Since the reductase from mammalian cells could be separated into its non-identical components (non-heme iron subunit and effector binding subunits), it was possible to show that these inhibitors are specifically directed toward only one of the subunits. It was shown that the inhibition of reductase by hydroxyurea, guanazole and IMPY was potentiated by the iron-chelating agents EDTA, Desferal and 8-hydroxyquinoline while the inhibition by MAIQ and IQ was reversed by the iron-chelating agents. Combinations of reductase inhibitors such as IMPY/dGTP, IMPY/Inox and hydroxyurea/dATP gave synergistic inhibition while combinations of MAIQ/IMPY and IMPY/hydroxyurea caused antagonistic effects. However, it was not possible to predict a priori which combinations would lead to the anticipated results. (Author abstract) (28 Refs)

12. INHIBITION OF GROWTH OF 3-METHYLCHOLANTHRENE-INDUCED MOUSE SKIN TUMOR BY PROTEASE INHIBITOR [N,N-DIMETHYLCARBAMOYLMETHYL 4-(4-GUANIDINOBENZOYLOXY)-PHENYLACETATE] METHANESULFATE.

Ohkoshi M

Dept. Oral Surgery, Nagoya Univ. Sch. Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya 466, Japan

Gan; 72(6):959-964 1981

A 3-Methylcholanthrene-induced tumor was challenged with a low molecular synthetic protease inhibitor, [N,N-dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy)-phenylacetate] methanesulfate. This drug at a dosage of 10 mg/kg or 20 mg/kg was administered by ip injection to 20 mice each harboring a solitary tumor twice daily for 10 wk. This protease inhibitor significantly inhibited tumor growth and prolonged the survival time of the tumor-bearing mice (p less than 0.001). The results suggest the involvement of kinin-forming proteases, such as trypsin, plasmin and kallikrein, in the tumor growth. (Author abstract) (16 Refs)

13. AUTORADIOGRAPHIC STUDY ON THE ROLE OF DIFFERENT RIBOSOME TYPES IN HUMAN LYMPHOBLASTS TREATED WITH VINBLASTINE.

Maraldi NM, Jovine R, Santi P, Papa S, Mazzotti G

Istituto di Morfologia Umana Normale, Cattedra di Istologia ed Embriologia, Generale Univ. Ancona, via Grotte di Posatora, Ancona, Italy

Cell Mol Biol; 27(5):483-489 1981

Human lymphoid cells have been treated in vitro with high doses of vinblastine sulfate which induce the formation of microtubule crystals surrounded by clusters of ribosomes and of isolated rows of granulofilamentous material associated with long regular polysome helices. The role of these ribosome associations, previously described in other cell types, has not been clarified. A high-resolution autoradiographic analysis has been made in order to determine whether these two types of ribosome associations are engaged in protein synthesis. The results indicate that the ribosomes associated with the microtubule crystals are active in protein synthesis and that the neosynthesized proteins are precipitated by the vinblastine in a crystalline form, while the regular polysomes are completely inactive since they are probably neosynthesized units transported along the cytoskeleton components. (Author abstract) (25 Refs)

14. EFFECT OF ADRIAMYCIN ON RAT HEART CELLS IN CULTURE: INCREASED ACCUMULATION AND NUCLEOLI FRAGMENTATION IN CARDIAC MUSCLE V. NON-MUSCLE CELLS.

Lampidis TJ, Johnson LV, Israel M

Div. Medical Oncology, Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115

J Mol Cell Cardiol; 13(10):913-924 1981

The mechanism of cardiotoxicity of adriamycin (ADR) was evaluated. A culture of heart cells from Sprague-Dawley rats was incubated with ADR at different doses and for various time periods. Fluorescence microscopy and flow cytometry examinations of cardiac cells treated with ADR at 10 ug/ml for 30 min showed significantly greater staining of cardiac muscle nuclei than non-muscle nuclei. The intensity of non-muscle nuclei fluorescence increased with increase in exposure, but the intensity of staining was consistently greater in the cardiac muscle nuclei. ADR induced nucleolar fragmentation in greater than 95% of muscle cells compared with less than 10% of non-muscle cells. After continuous incubation with ADR for 24 hr, all muscle and non-muscle cardiac cells showed nucleolar fragmentation. After treatment with non-DNA-binding ADR analog, fluorescence was observed in the cytoplasm of both muscle and non-muscle cardiac cells. (21 Refs)

15. THE REGULATION OF PROTEIN SYNTHESIS IN HEART MUSCLE UNDER NORMAL CONDITIONS AND IN THE ADRIAMYCIN-CARDIOMYOPATHY.

Zahringer J

Med. Klinik I, Klinikum Grosshadern, Marchioninistr. 15, D-8000 Munchen 70, W. Germany

Klin Wochenschr; 59(23):1273-1287 1981

The regulation of cardiac protein synthesis, in particular messenger-RNA (mRNA) and polyribosome metabolism, has been investigated in normal rat heart muscle and in the adriamycin-cardiomyopathy by using newly developed methods for the isolation, characterization and in vitro translation of cardiac polyribosomes and mRNA. (94 Refs)

16. INACTIVATION OF THE PLASMA PROTEASE INHIBITOR ALPHA2-MACROGLOBULIN BY THE ANTITUMOR DRUG CIS-DICHLORODIAMINEPLATINUM(II).

Gonias SL, Pizzo SV
Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
J Biol Chem; 256(23):12478-12484 1981

The plasma protease inhibitor alpha2-macroglobulin (alpha2M) was reacted in vitro with cis-dichlorodiamineplatinum(II) (cis-DDP). Following the reaction, alpha2M demonstrated a significantly decreased ability to bind trypsin as determined by esterase activity assays in the presence of soybean trypsin inhibitor and studies with radiolabeled trypsin. Inactivation of alpha2M by cis-DDP was not associated with a conversion to the 'fast' electrophoretic form, as determined on nondenaturing gels, in contrast to the inactivation of alpha2M by proteases and certain amine salts. The extent of reaction increased with the elevation of temperature within the thermal stability range of the protein; however, variation of pH within the range 6.82-8.55 had little effect. Binding of [14C]methylamine to alpha2M was not affected by cis-DDP. The conformational change, however, which normally accompanies this reaction did not occur. It is concluded that the alpha2M thiolesters are most likely not reactive sites for cis-DDP. cis-DDP-treated alpha2M failed to dissociate into quarter subunits under denaturing and reducing conditions, suggesting cross-linking of subunits. This cross-linking may be responsible for locking the alpha2M quaternary structure into the 'slow conformation.' (Author abstract) (41 Refs)

17. STUDIES OF THE LIMITING EFFECT ON MAMMARY TUMORS OF CIS-DICHLORO-BIS-(GLYCYLGLYCINE-ETHYLESTER) PLATINUM(II).

Seidenberger H, Kranzfelder G, Wappes B, Schonenberger H, Beck W, Girnth M
Institut fur Pharmazie der Universitat Regensburg, Universitatsstrasse 31, D-8400 Regensburg, W. Germany
Arch Pharm (Weinheim); 314(11):955-967 1981

The effects of cis-dichlorodiammine-platinum (II) and cis-dichloro-bis-(glycylglycine ethylester)-platinum (II) on mammary tumors were tested in vivo on tumors induced by dimethylbenzoanthracene in SD rats. Both compounds inhibited DNA synthesis and 3H-E2 receptor interaction. Inhibitory effects were due possibly to binding to DNA or estrogen receptors. (35 Refs) (In GER)

18. THE EFFECTS OF ADRIAMYCIN IN VITRO AND IN VIVO ON HEPATIC MICROSOMAL DRUG-METABOLIZING ENZYMES: ROLE OF MICROSOMAL LIPID PEROXIDATION.

Mimnaugh EG, Trush MA, Ginsburg E, Hirokata Y, Gram TE
Lab. Medicinal Chemistry/Biology, National Cancer Inst., Bethesda, MD, 20205
Toxicol Appl Pharmacol; 61(3):313-325 1981

The role of lipid peroxidation in the effects of adriamycin both in vitro and in vivo on microsomal cytochrome P-450, NADPH-cytochrome-c reductase, aminopyrine N-demethylase, UDP-glucuronyltransferase, and glucose-6-phosphatase activities was investigated. Male rats received 10 or 15 mg/kg of adriamycin ip 12, 24, or 48 hr prior to sacrifice; a separate group received 5 mg/kg of adriamycin ip 7, 4, and 1 day before sacrifice. Liver microsomes were then assayed for lipid peroxidation and cytochrome P-450; incubations to determine drug metabolizing enzyme activities were immediately conducted. Liver microsomes incubated with the NADPH generating system showed a 6x increase in lipid peroxidation. Microsomes preincubated with adriamycin and EDTA in the absence of the NADPH generating system showed a 35% decrease in cytochrome P-450 concentration and in aminopyrine activity. Both control NADPH- mediated and NADPH-dependent adriamycin-stimulated microsomal peroxidation reduced cytochrome P-450 content 85%, and inhibited aminopyrine demethylation 70%. UDP-glucuronyltransferase activity was increased nearly 5x by adriamycin-stimulated peroxidation; glucose-6-phosphatase activity was nearly abolished by lipid peroxidation. While acute adriamycin treatment had no significant effect on hepatic microsomal drug metabolizing enzymes, subacute injections appreciably depressed the activity. Lipid peroxidation was significantly increased after subacute injections. No change was observed in glucose-6-phosphatase or UDP-glucuronyltransferase activities. Adriamycin was apparently capable of impairing hepatic drug metabolism by stimulating membrane lipid peroxidation; the mechanism by which in vivo treatment decreased the activity of the drug mono-oxygenase system remains unclear. (53 Refs)

19. VINBLASTINE AND CYTOCHALASIN B EFFECTS ON DISTRIBUTION OF CONCANAVALIN A RECEPTORS IN NORMAL ATTACHED 3T3 CELLS.

Stefanini S, Temmink JH
Inst. Histology and Embryology, Univ. Rome, Rome, Italy
Cell Mol Biol; 27(4):333-339 1981

The effect of the antimicrotubule drug, vinblastine (VB), and of the antimicrofilament drug, cytochalasin B (CB), on the surface distribution of concanavalin A (ConA) binding sites was investigated on normal attached 3T3 cells. When labeled with ferritin-conjugated concanavalin A (Fer-ConA) or with ConA followed by horseradish peroxidase (ConA-HRP), normal 3T3 cells showed a slightly clustered distribution of ConA binding sites. These clusters were distributed randomly over the whole cell surface. This distribution of ConA-receptor complexes was not altered by treatment of cells with CB, despite the marked changes that this drug produced in cell morphology. On the other hand, treatment of 3T3 cells with VB produced marked changes, not only cell morphology, but also in the organization of ConA binding sites: ConA-receptor complexes were cleared from peripheral areas and moved towards the perinuclear part of the cell. The redistribution of ConA receptors is not dependent on VB treatment only, but also needs ConA binding, because in cells treated with VB and fixed before labeling with ConA, the redistribution does not occur. These results are discussed in relation with the role played by microtubules and microfilaments in redistribution of ConA binding sites. (Author abstract) (17 Refs)

20. ANTITUMOR ACTIVITY OF PICOLINIC ACID IN CBA/J MICE.

Leuthauser SW, Oberley LW, Oberley TD
(c/o Oberley) Radiation Res. Lab., Univ. Iowa, 14 Medical Lab., Iowa City, IA, 52242
JNCI; 68(1):123-126 1982

The growth of a solid tumor induced by im implantation of Ehrlich ascites tumor cells in inbred CBA/J mice was retarded by treatment with an iron chelator, picolinic acid (PLA). Survival of the mice was also significantly increased after PLA treatment. However, the iron chelator deferoxamine had no such effects; tumor growth was slightly enhanced, and survival was decreased. (Author abstract) (18 Refs)

21. INDUCTION OF DIFFERENTIATION OF HL-60 CELLS BY DIMETHYL SULFOXIDE: EVIDENCE FOR A STOCHASTIC MODEL NOT LINKED TO THE CELL DIVISION CYCLE.

Tarella C, Ferrero D, Gallo E, Pagliardi GL, Ruscetti FW

(c/o Ruscetti) Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205

Cancer Res; 42(2):445-449 1982

Induction of differentiation of the human promyelocytic leukemia cell line HL-60 by dimethyl sulfoxide (Me2SO) was analyzed to determine the relationship between exposure time of the inducer and cell cycle. A minimum incubation time of 12 hr with Me2SO was required in order to induce differentiation in a small but significant proportion of cells. These expressed differentiation markers (morpho logy, phagocytosis, and nitroblue tetrazolium reduction) up to 12 hr after Me2SO was removed from the medium. For periods beyond 12 hr and as long as 120 hr of contact of HL-60 cells with the inducing agent, a linear rise in the percentage of differentiated cells was observed. The sensitivity to Me2SO of HL-60 cells synchronized by double thymidine block was examined and was found to be similar to that of nonsynchronized cells. The effect of Me2SO was not altered when incubated with cells at different phases of the cell cycle. Finally, even nonproliferating cells were sensitive to the inducing effect of Me2SO. The data are consistent with a stochastic model of induction to differentiation without having any linkage to the cell cycle. (Author abstract) (29 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

22. CHLORPROMAZINE DISTRIBUTION IN HAMSTERS AND MICE BEARING TRANSPLANTABLE MELANOMA.

Fairchild RG, Greenberg D, Watts KP, Packer S, Atkins HL, Som P, Hannon SJ, Brill AB, Fand I, McNally WP

Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973

Cancer Res; 42(2):556-562 1982

Chlorpromazine (CPZ) distribution was measured in tissues of Syrian golden hamsters bearing Greene melanoma and in BALB/c mice bearing Harding-Passey melanoma. Distribution was evaluated as a function of time (0.5 to 14 days) and as a function of single and multiple doses (up to 5) of from 5 to 50 mg CPZ per kg body wt. Routes of administration (ip, iv, po) were compared. The physiological behavior of CPZ is of interest as it is used extensively as a tranquilizing drug (Thorazine). Further, since CPZ binds to the pigment melanin, the possibility exists of using CPZ to transport diagnostic or therapeutic agents to melanoma. It was found that, at 2 days postinjection, tumor/tissue concentration ratios exceeded 10 for metabolizing organs, such as liver, and 100 for 'background' tissues, such as blood and muscle. Absolute concentrations of CPZ in tumor exceeding 100 ug CPZ per g tumor were obtained with both single and multiple doses. This selective high concentration in tumor would make CPZ an ideal vehicle for the transport of boron to tumor for use in neutron capture therapy via the 10B(n,alpha)7Li reaction. (Author abstract) (37 Refs)

23. INFLUENCE OF PYRAZOFURIN ON THE TOXICITY AND ANTITUMOR ACTIVITY OF FLUORINATED PYRIMIDINES IN VIVO.

Johnson RK, Howard WS, Faucette LF, Wodinsky I, Clement JJ
Arthur D. Little, Inc., Cambridge, MA
Adv Enzyme Regul; 19:309-333 1981

We undertook to evaluate the interaction of pyrazofurin (PF) with another important pyrimidine antimetabolite, 5-fluorouracil (5-FU). 5-FU can be anabolized to the nucleoside monophosphate by three pathways, directly via phosphoribosylation by orotate phosphoribosyltransferase (EC 2.4.2.10), or via the salvage pathways, by either uridine phosphorylase (EC 2.4.2.3) and uridine kinas e or thymidine phosphorylase (EC 2.4.2.4) and thymidine kinase (EC 2.7.1.21). One might expect that depletion of pyrimidine nucleotides by PF might enhance the anabolism of 5-FU and allow for greater incorporation of 5-FU into RNA and/or lead to higher levels of 5-fluoro-2'-deoxyuridylate (FdUMP) with subsequent greater inhibition of thymidylate synthase (EC 2.1.1.45). This was, however, not the case. One the contrary, PF markedly decreased the toxicity of 5-FU and blocked its antitumor activity in some tumors as well. With the closely related compound, 5-fluorouridine (FUR), the interaction with PF was the opposite; there was a marked enhancement of both toxicity and antitumor activity similar to that seen with 5-ACr. (46 Refs)

24. SYNERGISTIC EFFECT OF CIS-DICHLORODIAMMINEPLATINUM AND 5-AZA-2'-DEOXYCYTIDINE ON MOUSE LEUKEMIC CELLS IN VIVO AND IN VITRO.

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Int J Cancer; 29(1):81-85 1982

The drugs cis-dichlorodiammineplatinum and 5-aza-2'-deoxycytidine display a considerable synergistic effect in L1210 and La mouse leukemia in vivo; the combination of both drugs is also clearly synergistic in vitro as evidenced by the effects on cell growth and cell survival in soft-agar medium. In exponential but not in stationary growth of L1210 cells, the drugs interfere with DNA and RNA synthesis. (Author abstract) (18 Refs)

25. EFFECTS OF HIGH-DOSE METHOTREXATE AND LEUCOVORIN ON MURINE HEMOPOIETIC STEM CELLS.

Pannacciulli I, Massa G, Bogliolo G, Ghio R, Sobrero A
Istituto Scientifico di Medicina Interna, Univ. Genoa, Viale Benedetto XV no. 6, 16132 Genoa, Italy
Cancer Res; 42(2):530-534 1982

This study compares the effects of a high dose of methotrexate (HDMTX) to that of a high dose of methotrexate plus leucovorin protection on the hemopoietic stem cells in a murine mode. C57BL x C3H F1 mice were treated with a single large bolus (500 mg/kg body wt) of methotrexate or with the same dose of the drug plus leucovorin administered in fractionated doses during the following 24 hr. At 1 to 2 days after the administration of HDMTX, there was a large bone marrow and spleen depopulation of pluripotent stem cells and of committed and recognizable progenitors. At 2 to 3 days, a severe fall of white blood cells and reticulocytes ensued. The recovery process of hemopoietic precursors followed alternate phases of overshooting and secondary falls. Leucovorin administration appeared to protect all stages of hemopoiesis and prevented the severe drops of bone marrow cellularity and stem cell content which followed the HDMTX bolus. However, the effect of leucovorin on peripheral blood cell reduction was less significant. After treatment with HDMTX, the recovery of bone marrow cells and the burst of splenic hemopoiet ic activity followed a pattern similar in both leucovorin-protected and unprotected animals, but in the former, the increase in stem cells and hemopoietic progenitors appeared to reach higher values and to last longer. In particular, the overshooting of colony-forming units, culture and erythroid, reached a higher peak in leucovorin-treated mice and was more prolonged. Our results indicate that, in HDMTX-treated mice, leucovorin protection involves the earliest stages of hemopoiesis, assuring the maintenance of a satisfactory endowment of stem and progenitor cells. (Author abstract) (28 Refs)

26. DOSE- AND SCHEDULE-DEPENDENT ACTIVATION AND DRUG SYNERGISM BETWEEN THYMIDINE AND 5-AZA-2'-DEOXYCYTIDINE IN A HUMAN PROMYELOCYTIC LEUKEMIA CELL LINE.

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Div. Hematology-Oncology, Columbia Presbyterian Medical Center, New York, NY, 10032
Cancer Res; 42(2):519-524 1982

The ability of thymidine (dThd) to enhance the metabolism and cytotoxicity of subsequently administered 5-aza-2'-deoxycytidine (5-aza-dCyd) was studied in L1210 cells and in the human promyelocytic leukemic cell line, HL-60. Exposure of L1210 cells to 0.1 mM dThd for 5 hr resulted in an increase in the total intracellular and acid-precipitable accumulation of 5-aza-dCyd. Higher dThd concentrations and longer exposure intervals resulted in smaller increments in 5-aza-dCyd accumulation. In contrast, in HL-60 cells, a 24-hr exposure to 1 mM dThd resulted in the greatest intracellular accumulation of 5-aza-dCyd, 3.3x more accumulation than in control cells. There was also a four-fold increase in the acid-precipitable accumulation and nearly a three-fold increase in DNA incorporation of 5-aza-dCyd in HL-60 cells exposed to the same dThd schedule. High-pressure liquid chromatographic analysis demonstrated a greater than three-fold increase in the intracellular amounts of 5-aza-dCyd metabolites eluting in the triphosphate region in these human cells under identical conditions. Shorter dThd incubation exposure intervals (6 hr) and lower dThd concentration (0.1 mM) produced smaller increments in these studies. Both growth inhibition and clonogenic assays of HL-60 cells demonstrated a dose- and schedule sequence-dependent synergism between dThd and 5-aza-dCyd. (Author abstract) (35 Refs)

27. INFLUENCE OF ADRIAMYCIN UPON THE IRRADIATION EFFECT ON CHINESE HAMSTER CELLS.

Trott KR, Meder G
Strahlenbiologisches Institut, Universitat Munchen, Bavariaring 19, D-8000 Munchen 2, W. Germany
Strahlentherapie; 157(4):265-271 1981

During combined treatment of Chinese hamster cells in vitro with adriamycin and irradiation, there appear interactions between the two treatment modalities, V79 cells showing interaction in an additive sense, B14 cells in the sense of synergistic interaction. The capacity for interaction can persist for a long while, and even may be transmitted to the offspring of surviving cells. Treatment with adriamycin does not influence the fractionation effect or the recovery from sublethal radiation damage in the case of following fractionated irradiation. (Author abstract) (12 Refs) (In GER)

28. EXPERIMENTAL COMBINATIONS OF CYTOTOXIC DRUGS AND RADIATION (MEETING ABSTRACT).

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Br J Radiol; 56(644):708 1981

There is now a large experimental literature on the combination of cytotoxic drugs and ionizing radiation. The great majority of studies have concentrated on (a) single doses of each agent, (b) experimentally accessible, ie rapidly renewing, normal tissues eg in gut, marrow and skin, and (c) intervals of a few hr between administration of modalities. For such intervals it has been possible to demonstrate (or infer) interactions between the effects of drugs and radiation in terms of altered capacity to accumulate or repair sublethal injury (actinomycin D (ACT-D), adriamycin (ADR), synchronization of cells surviving a first treatment (vincristine, VCR) or recruitment of resting cells into cycle (hydroxyurea, HU). Favorable and unfavorable intervals established for single doses may also apply for daily fractions, which we illustrate here by the response of the small intestine to VCR and gamma rays. However, we also show that within this time scale of hr, optimal timing varies quite markedly between different combinations, even for drugs with ostensibly the same cell-cycle phase specificity. The advantages to be gained in terms of normal-tissue sparing by increasing interval between courses of agents to days or even wk are discussed in terms of repopulation of cells and and of phenomena such as 'slow repair' in the lung (ADR). The constraint on this approach is the probability of regrowth of tumors which longer intervals might permit. Examples are cited of rapidly-growing rodent tumors for which longer intervals were actually advantageous in terms of tumor oxygenation. (no Refs)

29. TUMORICIDAL POTENTIAL OF NUTRITIONAL MANIPULATIONS.

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Cancer Res; 42(2,Suppl):756S-765S 1981

Perturbations of specific nutrient availability is the basis of a large number of chemotherapeutic modalities used in cancer treatment. The creation of transient nutrient deprivation states by deficient diets (deficiency), nutrient destruction or displacement (depletion), the presence of antimetabolites or analogs (deficiency state), or combinations of the above has shown significant antitumor effect in several animal and human cancers. Pair-fed isocaloric diets deficient in macronutrients such as carbohydrates (with or without gluconeogenesis inhibition) or micronutrients such as zinc or pyridoxine have demonstrated antitumor potential. Amino acid depletion by enzymes such as L-asparaginase or L-glutaminase has become a popular modality for treatment of human leukemias. Purine and pyrimidine analogs or folate antimetabolites have been used successfully for several decades in the treatment of human tumors. Excess pyridoxine in tissue culture has demonstrated antineoplastic potential. Dietetic supplementation with naturally occurring sugars, sugar derivatives, or analogs has also demonstrated tumorotropic effects. (Author abstract) (146 Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

30. IN VIVO KINETICS OF THYMIDYLATE SYNTHETASE INHIBITION IN 5-FLUOROURACIL-SENSITIVE AND -RESISTANT MURINE COLON ADENOCARCINOMAS.

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Cancer Res; 42(2):450-456 1982

The predictive utility of several biochemical parameters of 5-fluorouracil (5-FUra) action was evaluated in four murine colonic adenocarcinomas: 5-FUra-sensitive tumor 38 and 5-FUra-resistant tumors 07/A, 51, and 06/A. Thymidylate synthetase (TS) was determined by a tritiated 5-fluoro-2'-deoxyuridylate (FdUMP)-binding assay. Bolus 5-FUra (80 mg/kg, ip) administration caused in all tumors a rapid decrease in free TS levels. Only tumor 38, however, showed inhibition of TS to undetectable (less than 0.05 pmol/g) levels, which lasted up to 6 hr after treatment; correction for dissociation of endogenous TS; FdUMP:folate ternary complex during the TS assay was required. Total TS (free enzyme plus ternary complex) was determined with experimental conditions that achieved quantitative recovery of free TS from ternary complex. By 48 hr after 5-FUra, Tumor 38 showed a decrease in total TS proportional to the estimated log kill/dose of 5-FUra; in contrast, the resistant tumors showed no such decrease from pretreatment levels. Assay of FdUMP showed that the free nucleotide was formed rapidly in all tumors in excess over available TS-binding sites. However, tumor sensitivity did not correlate with peak or residual FdUMP levels or with deoxyuridylate levels, which were low and remained so in all tumors. Tumor sensitivity to 5-FUra also could not be explained by the small differences among the tumors in total perchloric acid-soluble metabolites of 5-FUra or drug incorporation into RNA. We conclude from these data that levels of free TS in the tumor after 5-FUra treatment are predictive of chemotherapeutic response in these murine models of human colonic adenocarcinoma. (Author abstract) (50 Refs)

31. THE ROLE OF SUBCELLULAR LOCALIZATION IN ASSESSING THE CYTOTOXICITY OF IODINE-125 LABELED IODODEOXYURIDINE, IODOTAMOXIFEN, AND IODOANTIPYRINE.

Bloomer WD, McLaughlin WH, Weichselbaum RR, Hanson RN, Adelstein SJ, Seitz DE
Dept. Radiation Therapy, Harvard Medical Sch., Boston, MA
J Radioanal Chem; 65(1/2):209-221 1981

The role of subcellular localization in the cytotoxicity of 125I-bearing compounds was studied in vitro in the MCF-7 cell line of human breast cancer, which was derived from a malignant pleural effusion. Cell cultures were exposed to 125I-labeled tamoxifen (125ITAM), 125I-iodoantipyrine (125IAP), or 125I-iododeoxyuridine (125IUdR) at various concentrations. Cellular uptake of 125IUdR and 125IAP was directly proportional to media concentration of the compounds, with 125IUdR being more avidly accumulated than 125IAP. 125IUdR was incorporated directly into the DNA backbone as a thymidine analog; 125IAP was distributed according to body water. Uptake of 125ITAM was time dependent, with a steep initial rise followed by a plateau at 20 min, 37 C; at 4 C uptake was less steep, but linear. Withdrawal of 125ITAM from the medium was followed by a rapid efflux of unbound intracellular (IC) 125ITAM, leaving about 20% of 125ITAM activity within the cell after 50 min. The retained IC activity represented specifically and nonspecifically bound 125ITAM. With survival measured as a function of media concentration, D37 values were 8 x 10(-4) uCi/ml for 125IUdR, 2.3 uCi/ml for 125ITAM, and 68 uCi/ml for 125IAP. With survival measured as a function of protein- or nucleic acid-bound fractions, 125ITAM was approx as toxic as 125IUdR. Results indicate the importance of considering subcellular localization in determining the cytotoxic effects of Auger-emitting compounds. (43 Refs)

32. REDOX CYCLING OF FE(III)-BLEOMYCIN BY NADPH-CYTOCHROME P-450 REDUCTASE.

Scheulen ME, Kappus H, Thyssen D, Schmidt CG
Dept. Internal Medicine (Cancer Res.), West German, Tumor Center Uniiv. Essen Medical Sch., 4300 Essen, W. Germany
Biochem Pharmacol; 30(24):3385-3388 1981

Reduction of Fe(III) by NADPH cytochrome P-450 reductase in the presence of bleomycin (BLM) was measured by NADPH oxidation (monitored by spectrophotometry). Enzymatic reduction of Fe(III)-BLM followed Michaelis-Menten kinetics, with Km = 5.2 x 10(-5) M BLM and Vmax = 2.0 x 10(-5) M/min. The role of NADPH cytochrome P-450 reductase in activation of Fe(III)-BLM was analyzed by determining the influence of various factors on DNA chain breakage. Active enzyme, oxygen, NADPH, BLM, and Fe(III) were essential for DNA degradation. Further study showed that DNA chain breakage by oxygen-Fe(III)-BLM , as catalyzed by NADPH cytochrome P-450 reductase, was inhibited by superoxide dismutase and augmented by catalase. Reduced glutathione and mannitol had no significant effect; and cupric ions could not substitute for ferric ions. These results favored the direct action on DNA of a superoxide anion radical released by the oxygen-Fe(III)-BLM complex. A proposed model of the Fe(III)-BLM redox cycle is similar to the cycle of quinone anticancer drugs. (21 Refs)

33. METABOLIC ACTIVATION AND CYTOTOXICITY OF CYCLOPHOSPHAMIDE IN PRIMARY CULTURES OF POSTNATAL RAT HEPATOCYTES.

Acosta D, Mitchell DB
Dept. Pharmacology, Coll. Pharmacy, Univ. Texas at Austin, Austin, TX, 78712
Biochem Pharmacol; 30(23):3225-3230 1981

We have developed a model of primary cultures of postnatal rat hepatocytes to characterize the metabolic activation of xenobiotics to toxic intermediates and to study the mechanism(s) by which these chemicals produce cellular injury. This model was employed to investigate the cytochrome P-450 mediated biotransformation of cyclophosphamide (CP) to cytotoxic metabolites that nonspecifically alkylate DNA and cellular proteins. The parenchymal cells were isolated by an in situ collagenase perfusion technique and cultured for 24 hr prior to drug treatment. The cultures were then exposed to CP concentrations ranging from 1 x 10(-4) M to 1 x 10(-3) M for 24 hr. Initial studies indicated minimal toxicity to non-replicating parenchymal hepatocytes maintained in ornithine-supplemented, arginine-deficient medium. The addition of arginine permitted the overgrowth of fibroblasts in the same culture system. These fibroblasts then became the target of alkylating CP metabolites produced by the parenchymal cells. By day 3 after CP administration, cell number and total protein per dish decreased by over 40%. The morphology of the cultures changed dramatically because of fibroblast destruction. The cytotoxicity to dividing fibroblasts was eliminated by administering 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF 525-A), an inhibitor of the cytochrome P-450 monooxygenase system, to the co-cultures treated with CP. The alkylating metabolites of CP produced by parenchymal cells and released into the culture medium were quantitated by reacting aliquots of medium from CP-treated cells with 4-(p-nitrobenzyl)pyridine. These results provide both direct and indirect evidence of drug metabolism in cultured cells and suggest that this co-culture system can be utilized to evaluate the metabolic activation of xenobiotics. (Author abstract) (49 Refs)

34. FOLATE CATABOLISM IN TUMOUR-BEARING RATS AND RATS TREATED WITH METHOTREXATE.

Saleh AM, Pheasant AE, Blair JA
Dept. Chemistry, Univ. Aston Birmingham, Birmingham B4 7ET, England
Br J Cancer; 44(5):700-708 1981

The metabolism of (2-14C) + (3',5',7,9-3H) folic acid was studied in normal rats, tumor-bearing rats and rats treated with methotrexate (MTX). The experiments were designed to investigate changes in the catabolism of folate. The breakdown of folate to scission products was again demonstrated to be a normal phenomenon. Catabolites excreted included p-acetamidobenzoate, p-acetamidobenzoyl-L-glutamate, 3H2O, urea and a number of pterins. The catabolic process was decreased in the presence of a tumor and increased by the administration of MTX. MTX also led to the excretion of four additional radioactive pterins not found in normal urine. The possible mechanisms of folate breakdown are discussed with reference to the point of action of MTX. (Author abstract) (41 Refs)

35. METABOLISM OF 5-FLUOROURACIL IN VARIOUS HUMAN NORMAL AND TUMOR TISSUES.

Maehara Y, Nagayama S, Okazaki H, Nakamura H, Shirasaka T, Fujii S
Div. Regulation of Macromolecular Function, Inst. Protein Res., Osaka Univ., 5311 Yamada Oka, Suita 565, Japan
Gan; 72(6):824-827 1981

The metabolism of 5-fluorouracil (5-FU) in tumors and normal tissues of humans was investigated in vitro. Phosphorylation of 5-FU was faster in tumor tissues than in normal tissues. Phosphorylating activity with 2-deoxy-alpha-D-ribose 1-phosphate (dRiblP) and ATP as cofactors was more active than that with alpha-D-ribose 1-phosphate (RiblP) and ATP, or 5-phospho-alpha-D-ribosyldiphosphate (PPRibP) as cofactors. Phosphorylating activity in squamous cell carcinoma of the lung was similar to that in adenocarcinomas. Degradation of 5-FU was much faster in the liver than in other tissues including tumor tissues. (Author abstract) (27 Refs)

36. INTERACTIONS AMONG IRON(II) BLEOMYCIN, LEWIS BASES, AND DNA.

Antholine WE, Petering DH, Saryan LA, Brown CE
Radiation Biology and Biophysics Section, Medical Coll. Wisconsin, Milwaukee, WI, 53226
Proc Natl Acad Sci USA; 78(12):7517-7520 1981

The interaction of sulfur-containing ligands with complexes of Fe(II) bleomycin [Fe(II)Blm] was investigated by comparing DNA strand-scission activity with the structural characteristics of the complex. The bithiazole ring of excess Blm can form intermolecular complexes with Fe(II)Blm and with NO-Fe(II)Blm, and the bithiazole groups of CO-Fe(II)Blm interact with the metal center. This binding can be reversed by glutathione. CO-Fe(II)Blm binds to poly(dA-dT)poly(dA-dT) via its bithiazole group to change the environment of the Fe++ ion. Glutathione binds to the CO-Fe(II)Blm-poly(dA-dT)-poly(dA-dT) complex under conditions in which it stimulates DNA strand scission by Fe(II)Blm. (Author abstract) (21 Refs)

37. DISPOSITION AND METABOLISM OF 1-(2-CHLOROETHYL)-3-(2',3',4'-TRI-O-ACETYL, RIBOPYRANOSYL)-1-NITROSOUREA IN RATS.

Godeneche D, Moreau MF, Madelmont JC, Duprat J, Plagne R
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Cancer Res; 42(2):525-529 1982

The antineoplastic activity in animals of 1-(2-chloroethyl)-3-(2',3',4'-tri-O acetyl,ribopyranosyl)-1-nitrosourea (RPCNU) has been widely demonstrated. The present study deals with the disposition and the metabolism in rats of three 14C-labeled species of RPCNU. The chemical plasma half-life of the drug was less than 5 min. Within the first min after injection, most of the radioactivity derived from ethyl-14C groups was recovered as volatile products. Among these, 2-chloroethanol was identified as a main component. Analysis of labeled species in urine after administration of [ethyl-14C]RPCNU showed that thiodiacetic acid and its sulfoxide were major metabolites of RPCNU (62% of the urinary radioactivity). Traces of N-acetylcarboxymethyl- and N-acetyl-hydroxyethylcysteine were also detected. The only labeled species concentrating in particular tissues was that carrying the chloroethyl moiety. Uptake to high levels of [ethyl-14C]RPCNU did occur in liver, kidney, pancreas, thymus, and Harder's gland. (Author abstract) (22 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

38. ANTITUMOR ACTIVITY OF N-DIAZOACETYL DERIVATIVES OF GLYCINE AND PHENYLALANINE AGAINST P388 LEUKEMIA AND B16 MELANOMA IN MICE.

Sava G, Giraldi T, Baldini L
Istituto di Farmacologia, Universita degli Studi di Trieste, Via A. Valerio N 32, 34100 Trieste, Italy
Cancer Treat Rep; 66(1):179-181 1982

N-Diazoacetyl derivatives of glycine and phenylalanine show antitumor activity in mice bearing P388 leukemia or B16 melanoma. The presented data indicate that antitumor activity is shown by diazomethylamide derivatives of glycine and phenylalanine, in addition to that already established for the amino acid derivatives having an O-diazoacetyl group (azaserine) or a diazoketone structure (DON and azotomycin) and for 1,2-bis-diazoacetyl ethane. (Author abstract) (15 Refs)

39. REGULATION OF RIBONUCLEOTIDE REDUCTASE IN MAMMALIAN CELLS BY CHEMOTHERAPEUTIC AGENTS.

Elford HL, Van't Riet B, Wampler GL, Lin AL, Elford RM
Dept. Biochemistry, MCV/VCU Cancer Center, Medical Coll. Virginia, Richmond, VA, 23298
Adv Enzyme Regul; 19:151-168 1981

The reductive conversion of ribonucleotides to deoxyribonucleotides is a prime target for the development of a cancer chemotherapeutic agent. A new series of inhibitors based on the polyhydroxy or polyamino aromatic ring has been developed. These compounds are effective ribonucleotide reductase inhibitors and possess antitumor activity if there are adjacent hydroxy or amino groups. The most effective enzyme inhibitor, 2,3,4-trihydroxybenzohydroxamic acid, is 145x more effective than hydroxyurea. However, the best antileukemic compound is 3,4-dihydroxybenzohydroxamic acid, which increased the life span of L1210 leukemic mice more than 100%. Structure-activity studies have revealed that the hydroxamic moiety is not essential for activity. The polyhydroxybenzene derivatives reduced the pool sizes of all four deoxynucleotides. This contrasts with the action of hydroxyurea, which depletes only the deoxypurines. The mechanism of inhibition by this group of compounds appears to be related to their ability to trap free radicals, since there is good correspondence between reductase inhibition and free radical destruction. Some naturally occurring cytotoxic and neurological agents which have antineoplastic activity, dopa analogs and phenolic compounds isolated from mushrooms, bear a structural similarity to the new reductase inhibitors. We found that the dopa analogs were also inhibitory to ribonucleotide reductase. Another consequence of polyhydroxybenzoic acid derivative treatment is elevated reductase levels in the cell. Other cell cycle inhibitors that block from late G1 through early G2 also cause an enhanced level of ribonucleotide reductase. However, agents that block in early or mid-G1 or mid or late G2 and mitosis produce lower reductase levels. These data suggest that reductase synthesis is initiated at the G1/S transition point and this enhanced level of activity continues until late S or G2. (Author abstract) (43 Refs)

EFFECTS OF ANTIMETASTATIC AGENTS

40. INVOLVEMENT OF MACROPHAGES IN THE ERADICATION OF ESTABLISHED METASTASES FOLLOWING INTRAVENOUS INJECTION OF LIPOSOMES CONTAINING MACROPHAGE ACTIVATORS.

Fidler IJ, Barnes Z, Fogler WE, Kirsh R, Bugelski P, Poste G
Cancer Metastasis and Treatment Lab., NCI-Frederick Cancer Res. Facility, Frederick, MD, 21701
Cancer Res; 42(2):496-501 1982

Liposomes containing encapsulated lymphokines or muramyl dipeptide (MDP), when injected iv into C57BL/6 mice, produce significant destruction of established lung and lymph node metastases from a sc highly metastatic B16-BL6 melanoma. We present evidence that eradication of the metastases is mediated by the activation of host macrophages to the tumoricidal state. Results from three separate types of experiments support this conclusion. (a) When macrophage-activating agents such as lymphokines or MDP were delivered in liposomes that were not efficiently retained in the lung, little or no activation of lung macrophages was observed, and growth of metastases was unaltered. (b) Eradication of metastases was not observed when tumor-bearing animals were treated with agents that impaired macrophage function (eg, silica, carrageenan, hyperchlorinated drinking water) prior to systemic therapy with liposome-encapsulated lymphokines or liposome-encapsulated MDP. (c) Macrophages activated in vitro by liposome-encapsulated MDP and then injected iv into mice bearing experimental lung metastases also significantly inhibited lung metastases. These results suggest that the augmented host response against pulmonary and lymph node metastases generated by the systemic administration of liposome-encapsulated lymphokines or MDP is mediated via activated cytotoxic macrophages. (Author abstract) (44 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

41. ANTITUMOR AGENTS FROM STREPTOMYCES ANANDII: GILVOCARCINS V, M AND E.

Balitz DM, O'Herron FA, Bush J, Vyas DM, Nettleton DE, Grulich RE, Bradner WT, Doyle TW, Arnold E, Clardy J
Res. Div., Bristol Lab., Div. of Bristol-Myers Co., Syracuse, NY, 13201
J Antibiot (Tokyo); 34(12):1544-1555 1981

The isolation and structure elucidation of gilvocarcins V, M and E from Streptomyces anandii is reported. Solvent extraction and high performance liquid chromatography were employed along with NMR and x-ray crystallographic analysis. Gilvocarcins V and M showed antimicrobial activity while only gilvocarcin V demonstrated potential as an antitumor agent. (Author abstract) (11 Refs)

42. THIOXACARCINS, NOVEL ANTITUMOR ANTIBIOTICS. II. ISOLATION, PHYSICO-CHEMICAL PROPERTIES AND MODE OF ACTION.

Tamaoki T, Shirahata K, Iida T, Tomita F
Tokyo Res. Lab., Kyowa Hakko Kogyo Co. Ltd., Machida, Tokyo, Japan
J Antibiot (Tokyo); 34(12):1525-1530 1981

Novel antitumor antibiotics, trioxacarcin complex, were isolated from the fermentation broth of Streptomyces bottropensis DO-45 by the use of non-ionic porous resin and silica gel chromatography. The purified components (trioxacarcins A, B and C) were characterized as new antibiotics by their physicochemical properties and chromatographic behaviors. The mode of action of trioxacarcin A against Bacillus subtilis was found to be through the inhibition of DNA synthesis. (Author abstract) (5 Refs)

43. TRIOXACARCINS, NOVEL ANTITUMOR ANTIBIOTICS. I. PRODUCING ORGANISM, FERMENTATION AND BIOLOGICAL ACTIVITIES.

Tomita F, Tamaoki T, Morimoto M, Fujimoto K
Tokyo Res. lab., Kyowa Hakko Kogyo Co. Ltd., Machida, Tokyo, Japan
J Antibiot (Tokyo); 34(12):1519-1524 1981

A group of antitumor antibiotics with a novel skeleton, trioxacarcins, was discovered in culture broths of actinomycete strain DO-45. The producing organism was subsequently determined to be a new strain and named Streptomyces bottropensis DO-45. The antibiotics are active against Gram-positive bacteria and experimental murine tumors such as sarcoma 180 and leukemia P388. (Author abstract) (9 Refs)

INTERFERON AND OTHER ANTIVIRALS

44. ASSAYS TO MEASURE PLASMA MEMBRANE AND CYTOSKELETAL CHANGES IN INTERFERON-TREATED CELLS.

Pfeffer LM, Wang E, Landsberger FR, Tamm I
Rockefeller Univ., New York, NY, 10021
Methods Enzymol; 79:461-473 1981

Techniques were described for the measurement of interferon (IF)-induced changes in cell size, cytoskeleton, cell surface fibronectin distribution, lateral mobility of cell surface receptors, and fluidity of the plasma membrane. Cell surface area of human diploid fibroblasts (between passages 10-20) was measured with the use of photomicrographs; cell vol was determined by a Coulter H4 Channelyzer. Cells treated with IF were more heterogeneous than control cells as indicated by greater coefficient of variation (21.5% vs 11.5%) of the cell vol distribution. Indirect immunofluorescence staining of microtubules, 10-nanometer filaments, microfilaments, and fibronectin of human fibroblasts was also discussed. Human HeLaS3 cells were used to show the effect of IF on lateral mobility of cell surface receptors for fluorescein-conjugated concanavalin A, which was examined by epifluorescence microscopy. In IF-treated cells incubated at 37 C, the fluorescence remains patchy and does not tend to form a cap, as occurs in control cells. The use of electron spin resonance techniques plus probe molecules (spin labels) to study the influence of IF on structure of the plasma membrane lipid bilayer in HeLaS3 cells and human fibroblasts was also discussed, with comments on some technical details and interpretation of the resulting spectra. (20 Refs)

45. INTERFERON 1981. PRESENT STATUS OF RESEARCH AND THERAPEUTIC USE.

Borecky L
Virologicky ustav, SAV, 809 39 Bratislava 9, Czechoslovakia
Cas Lek Cesk; 120(44):1329-1337 1981

Marked acceleration and even fundamental change in the production, as well as in the biochemical, functional and genetic characterization and classification of interferons were seen in 1981. However, the results of thorough therapeutic trials were disappointing. Tumor induction by interferon in NZB/W mice was observed. (26 Refs) (In SLO)

46. INTRACELLULAR PRODUCTION OF VIRUS PARTICLES AND VIRAL COMPONENTS IN NIH/3T3 CELLS CHRONICALLY INFECTED WITH MOLONEY MURINE LEUKEMIA VIRUS: EFFECT OF INTERFERON.

Aboud M, Kimchi R, Bakhanashvili M, Salzberg S
Microbiology and Immunology Unit, Faculty of Health Sciences, Ben-Gurion, Univ. Negev, Beer-Sheva, Israel
J Virol; 40(3):830-838 1981

The effect of interferon on the biochemical properties and the maturation process of intracellular viral particles isolated from the cytoplasmic fraction of NIH/3T3 cells chronically infected with Moloney murine leukemia virus was investigated. By labeling these virions with either [35S]methionine or [3H]glucosamine, we demonstrated that they contain the same viral proteins and glycoproteins found in extracellular virions. Interferon treatment was found to reduce the rate of intracellular virus assembly. This effect was not a consequence of an interferon inhibition of viral RNA synthesis or its translation or a consequence of an interference with the posttranslational cleavage processing of viral precursor proteins, since all of these steps were not affected by interferon. However, the reduced rate of virus assembly could be attributed to the inhibition of viral protein glycosylation observed in interferon-treated cells. Nevertheless, despite this reduced rate, virus particles accumulated in interferon-treated cells. This accumulation was probably due to the strong inhibition of their final release from such cells. (Author abstract) (39 Refs)

47. REVIEW OF EXPERIENCE WITH INTERFERON AND DRUG SENSITIVITY TESTING OVARIAN CARCINOMA IN SEMISOLID AGAR CULTURE.

Epstein LB, Marcus SG
Cancer Res. Inst., Univ. California, San Francisco, CA, 94143
Cancer Chemother Pharmacol; 6(3):273-277 1981

Studies were performed with a semisolid agar culture system to determine the in vitro sensitivity of human ovarian carcinoma to human leukocyte interferon (IFN-alpha) and standard chemotherapeutic agents (adriamycin, cis-platinum, hexamethylmelamine, melphalan, and velban). Growth in culture occurred in 67% of samples derived from ascitic fluid. Seventy-one percent of samples exhibited reduction in tumor colony number greater than 25% in response to 300 units IFN/ml. The responsiveness of the tumor cells to interferon ran parallel to their overall responsiveness to the other chemotherapeutic agents. Sensitivity to interferon was not related to the histology or grade of the tumor or to the stage of the disease. The mean value for the percentage of viable cells in the ascitic samples (89%) was considerably higher than in solid tumor samples (39%). The mean percentage of tumor cells in the ascitic samples (28%) was considerably lower than of the solid tumor samples (81%). Colonies from ascitic fluid were more sensitive to the antiproliferative effects of interferon than the colonies form solid tumor samples. Analysis of drug testing showed that in 58% of 12 evaluable situations when a positive response in vitro was given, stabilization or regression of the tumor occurred in vivo after treatment with the drug. The studies could be used for assessing whether various types of interferon have the same degree, range, and mechanism of action of antitumor effect. (18 Refs)

48. ENHANCED EXPRESSION OF MELANOMA-ASSOCIATED ANTIGENS AND BETA2-MICROGLOBULIN ON CULTURED HUMAN MELANOMA CELLS BY INTERFERON.

Liao SK, Kwong PC, Khosravi M, Dent PB
Dept. Pathology, Health Sciences Centre, McMaster Univ., 1200 Main St. West, Hamilton, Ontario L8N 3Z5, Canada
JNCI; 68(1):19-25 1982

The effect of human leukocyte interferon (IFN) on the in vitro growth and expression of melanoma-associated antigens (MAA), beta2-microglobulin (beta2m) and HLA-DR antigen on cultured human melanoma cells was studied. Exposure of melanoma cells to IFN for 64 hours resulted in a dose-dependent inhibition of growth with 46% reduction in cell number at 10(3) U IFN/ml and 74% reduction at 10(5) U/ml. Quantitative absorption experiments in the mixed hemadsorption assay determined that the expression of MAA and beta2m on treated cells was enhanced at 10(2) -10(5) U IFN/ml, twofold to fivefold for MAA and fiv efold to twelvefold for beta2m. No change was seen in HLA-DR antigen expression. The IFN-induced enhancement of MAA and beta2m could be detected as early as after 16 hours and a maximum expression was reached at 96 hours after IFN exposure. The IFN-induced enhancement of MAA and beta2m on melanoma cells was reversible. Studies with melanoma cells grown in stationary phase and serum-deprived conditions indicated that IFN-induced augmentation of MAA and beta2m did not require cell proliferation. The data suggest that the effect of IFN on antigen expression is independent of its effect on cell growth. Further studies are needed to fully elucidate the mechanism. (Author abstract) (42 Refs)

49. RAID SYNCYTIUM FORMATION INDUCED BY MOLONEY MURINE SARCOMA VIRUS IN 3T3/NIH CELLS AND ITS DELAY BY MOUSE INTERFERON.

Aboud M, Huleihel M
Unit Microbiology and Immunology, Faculty Health Sciences, Ben Gurion Univ. Negev, Beer Sheba, Israel
Arch Virol; 70(2):103-114 1981

Moloney murine sarcoma virus (MSV) clone 124 was found to induce rapid syncytium formation upon infection of 3T3/NIH at a high multiplicity of infection. This effect became apparent, by light microscopy, within 1 to 2 hr, whereas by scanning electron microscopy, clusters of 4 to 25 cells were seen in their initial steps of syncytium formation within 20 to 30 min after virus addition. It appeared that the cell fusion was initiated by connection between the cells through virus bound to their surface. After a few more hr several neighboring syncytia fused into giant cells containing over a hundred nuclei. Though MSV (124) stocks contained also some MLV it appeared that the syncytium inducing activity was related to the MSV particles. MLV particles were not only incapable to induce syncytium formation, they even interfered with this activity of MSV. The MSV-induced cell fusion required the adsorption of intact virions, but was independent on protein synthesis. Mouse interferon remarkably reduced the rate of syncytium development. (Author abstract) (40 Refs)

50. LACK OF INTERFERON-INDUCED TRANSFER OF VIRAL RESISTANCE AGAINST MURINE LEUKEMIA VIRUS OR POLIOVIRUS IN COCULTIVATED CELLS.

Mozes LW
Papanicolaou Cancer Res. Inst., Miami, FL, 33101
Virology; 116(1):359-362 1982

It has recently been reported that there can be a transfer of the interferon (IFN)-induced viral resistance between cocultivated animal cells. However, in those systems the challenge virus was capable of replicating in both cell types. A more convincing conclusion could be obtained if the infecting virus could not replicate in the cell type which is homologous to the species of IFN that is added to the cultures. An inhibition of the yield of this virus would indicate that there was a transfer of the antiviral state from one cell species to another. In cocultivated mouse and human cells, a murine ecotropic Type-C vir us can only multiply in the mouse cells whereas poliovirus will only replicate efficiently in the human cells. It is clearly evident from this study that only homologous but not heterologous fibroblast IFN is capable of inhibiting the replication of either of these viruses in various combinations of cocultivated cells. (Author abstract) (13 Refs)

51. ANALYSIS OF INTERFERON MRNA IN HUMAN FIBROBLAST CELLS INDUCED TO PRODUCE INTERFERON.

Raj NB, Pitha PM
Oncology Center, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Proc Natl Acad Sci USA; 78(12):7426-7430 1981

The levels of interferon mRNA as a function of interferon induction by poly(rI)-poly(rC) in human fibroblast cells were determined by RNA hybridization using a cloned beta interferon cDNA and by translation in Xenopus oocytes. Whereas previous studies analyzed mixtures of interferons, the availability of the cloned beta interferon cDNA and the antiserum to purified beta interferon enabled us to focus on the expression of only one class (beta) of interferon genes. The induction of interferon synthesis depends primarily on the accumulation of interferon beta mRNA in the cells, and the interferon beta mRNA rapidly disappears several hours after its appearance in the cytoplasm. No detectable interferon beta mRNA sequences are present in uninduced cells. The degradation of interferon beta mRNA in the induced cells requires ongoing protein synthesis; accumulation of interferon beta mRNA was observed in the continuous presence of cycloheximide. The interferon beta mRNA detected at the early stages of induction is 1,100 nucleotides long and its size progressively decreases with time. By both the hybridization and the translational assay in Xenopus oocytes, only one size of interferon beta mRNA and one species of beta interferon could be identified. (Author abstract) (33 Refs)

52. IN VITRO AND IN VIVO INHIBITION OF MYXOMA VIRUS BY TREATMENT WITH PHOSPHONOACETIC ACID.

Goodrich JM, Lee KW, Hinze HC
Rush Medical Coll., Chicago, IL
Arch Virol; 70(2):157-164 1981

Both myxoma and fibroma viruses were found to be sensitive in vitro to the effects of phosphonoacetic acid. Detectable myxoma virus replication was inhibited at a drug concentration of 100 ug/ml. Fibroma virus replication was inhibited at a concentration of 500 ug/ml. Because of this difference in sensitivity, myxoma virus was used to infect rabbits to test the efficacy of phosphonoacetic acid in the treatment of a systemic viral disease. Rabbits were given 400 mg kg-1 day-1 of phosphonoacetic acid sc in two injections. Phosphonoacetic acid-treated animals showed a reduction in the severity of disease. Neither serum viral antigen nor infectious virus could be detected. In phosphate buffered saline-treated animals both serum viral antigen and infectious virus were found. All animals treated with phosphate buff ered saline died of myxomatosis. (Author abstract) (23 Refs)

53. PROCEDURES TO STUDY THE CYTOSTATIC EFFECTS OF INTERFERON ON EHRLICH ASCITES CELLS.

Nagano Y, Saito H
Natl. Sagamihara Hosp., Sagamihara 228, Japan
Methods Enzymol; 79:360-361 1981

Media, equipment, and techniques are given for determining the inhibitory effect of interferon (IF) from mouse L-929 cells on Ehrlich ascites (EA) cells. The EA cells in the present experiment were STD-ddY mouse passage cells, which were used for viable- and dead-cell counts and mitotic index. Other experiments measured the inhibitory effect of cycloheximide and high temperature (39 C) in conjunction with IF. (3 Refs)

54. MEASUREMENT OF INTERFERON EFFECTS ON MURINE LEUKEMIA VIRUS (MULV)-INFECTED CELLS.

Pitha PM
Biochemical Virology Lab., Johns Hopkins Oncology Center, Baltimore, MD, 21205
Methods Enzymol; 79:422-432 1981

Assays of infectious murine leukemia virus (both ecotropic and xenotropic), suitable for measuring interferon effects, are reviewed. Cell-free virus assay, infectious centers assay, in situ infectious assay, and syncytia induction in XC cells (rat tumor line) are described for ecotropic viruses. For xenotropic viruses, the assay for MSV (murine sarcoma virus), virion-associated reverse transcriptase, radioisotope labeling of virus particles, and virus purification, are discussed. Chromatographic purification of viruses, isolation of virus RNA and its analysis by gel electrophoresis, and separation and identification of virion proteins are reviewed. Assays of viral RNA and protein in infected cells, including methods of preparation, nucleic acid hybridization, northern blotting technique, and competitive radioimmunoassay, are also reviewed. (32 Refs)

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EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. MELPHALAN PREVENTS THE FORMATION OF DOUBLE-STRANDED DNA REPLICATION INTERMEDIATES IN HUMAN MALIGNANT MELANOMA CELLS.

Lonn U, Lonn S

Dept. Histology, Karolinska Institutet, P.O. Box 60400, S-104 01 Stockholm, Sweden

Carcinogenesis; 2(12):1311-1316 1981

When human melanoma cells are lysed in a neutral buffer they release from the chromosomes double-stranded DNA replication intermediates. We have now examined the effect of a bifunctional alkylator (melphalan) on the formation of these intermediates. After treatment for 25 min there is little or no release of double-stranded DNA intermediates from the chromosomes. When the cells are washed free of the drug and cultivated further there is a resumed formation of the DNA intermediates. This is paralleled by the finding that the cells, when the drug is removed, after a time-lag, regain the capacity to proliferate. (Author abstract) (7 Refs)

2. EFFECT OF ANTINEOPLASTIC ANTIBIOTIC ACTINOXANTHINE ON CELLS GROWING IN VITRO.

Borodina VM, Kir'ianova EA, Zelenin AV, Reshetov PD, Chupova LA

Inst. Molecular Biology, Moscow, USSR

Antibiotiki; 26(12):915-919 1981

Biological activity of antineoplastic antibiotic actinoxanthine (AX) was studied in cultured murine L fibroblasts. Cells growing in a monolayer were treated with AX at 1-50 ug/ml. Fluorescence microscopy showed marked changes in the cell nuclei (formation of chromatin bodies, shifting of chromatin bodies towards the nuclear membrane, decrease of the number of nucleoli). The changes in the morphology of cell nuclei depended upon the AX concentration and the duration of exposure. Cytofluorimetric analysis showed a 40% decrease of DNA synthesis in cells treated with AX. Autoradiography showed a 70-80% inhibition of RNA synthesis. AX at 50 ug/ml caused complete inhibition of mitotic activity. AX did not affect the cell membranes of lysosomal membranes. (16 Refs) (In RUS)

3. INTERACTION OF ANTINEOPLASTIC ANTIBIOTIC OLIVOMYCIN WITH MG++ IONS.

Pitina LR, Baranov EP, Grinchenko BI, Brikenshtein BKh, Barenboim GM

Res. Inst. Biological Testing of Chemical Substances, Kupavna, Moscow Oblast', USSR

Antibiotiki; 26(12):906-912 1981

To evaluate the mechanism of selective effect of antineoplastic antibiotic olivomycin (OM) on the DNA molecule, the interaction of OM with Mg++ was studied. Fluorescence analysis showed a two-stage complex-formation. Determination of the kinetic parameters of OM-Mg++ interaction showed that formation of the stable complex was associated with a 10x decrease of the quantum yield of the fluorescence. (15 Refs) (In RUS)

4. MOLECULAR MECHANISMS OF BINDING AND SINGLE-STRAND SCISSION OF DEOXYRIBONUCLEIC ACID BY THE ANTITUMOR ANTIBIOTICS SAFRAMYCINS A AND C.

Lown JW, Joshua AV, Lee JS

Dept. Chemistry, Univ. Alberta, Edmonton, Alberta T6G 2G2, Canada

Biochemistry; 21(3):419-428 1982

The quinone antitumor antibiotics saframycins A and C bind to duplex DNA and G,C containing complementary oligodeoxyribonucleotides of pHs below 5.5 via selective protonation of the antibiotics at the N-12 positions in an equilibrium process. This binding shows minor groove specificity to T4 DNA for both antibiotics. Saframycin A exhibits an additional mode of covalent binding to DNA, which is reversible by heating, via an animal linkage with the NH2 group of guanine. Covalent binding of saframycin A is enhanced by prior reduction of the quinone moiety via a different mechanism with concomitant elimination of the nitrile group and plausibly involves an intermediate quinone methide. Both saframycin A and saframycin C were reduced in situ with NADPH or sodium borohydride cause single-strand breaks, but not double-strand breaks, in PM2 covalently closer circular DNA. This latter reaction proceeds via intermediate semiquinones, the identity and conformation of which are established by EPR. The DNA scission process which requires oxygen is mediated by the generation of O2-, H2O2 and OH, the latter of which species was identified by spin trapping. The strand scission of DNA is pH dependent and, unlike the binding of the antibiotics, is strongly inhibited by Mg++ and Zn++ ions. (Author abstract) (37 Refs)

5. DEGRADATION OF HELA CELL CHROMATIN BY NEOCARZINOSTATIN AND ITS CHROMOPHORE.

McHugh MM, Woynarowski J, Beerman T

(c/o Beerman) Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263

Biochim Biophys Acta; 696(1):7-14 1982

Chromatin is the in vivo target site for neocarzinostatin, a DNA strand scission antitumor drug. The effect of neocarzinostatin and its active chromophore component on HeLa cell chromatin is described here. Chromatin consisting of a mixture of mono-, di-, tri- and larger nucleosome fragments is prepared by micrococcal nuclease digestion of HeLa cell nuclei. Drug-induced conversion of chromatin to smaller sized fragments is measured by electrophoresis of the DNA on non-denaturing 4% polyacrylamide gels. Chromatin breakdown measured under these conditions is double-stranded in nature. In the presence of 2 mM dithiothreitol, neocarzinostatin causes degradation of large chromatin fragments and a loss of distinct nucleosome peaks. Detection of chromatin breakdown by neocarzinostatin is dependent upon the concentration of chromatin in the assay. When chromatin is increased from 14 to 70 ug/ml, changes in the larger fragments caused by 100 ug/ml neocarzinostatin become less obvious and are almost undetectable at 140 ug/ml chromatin. No change is observed when chromatin is treated with either neocarzinostatin or its chromophore in the absence of dithiothreitol. For detectable levels of chromatin degradation, 10 ug/ml neocarzinostatin is required compared to only 2.5 ug/ml chromophore (expressed in ug equivalent neocarzinostatin). Such degradation also occurs more rapidly with chromophore than with neocarzinostatin. Digestion of chromatin with neocarzinostatin continues for at least 30 min at 37 C, while similar degradation caused by chromophore is complete in 1 min. Neocarzinostatin levels which actively degrade isolated chromatin can also effect release of soluble chromatin from intact nuclei. The released chromatin can serve as a substrate for micrococcal nuclease digestion. Such chromatin studies should prove useful in characterizing the mechanism of action of DNA reactive drugs such as neocarzinostatin. (Author abstract) (29 Refs)

6. STRAND SCISSION OF DEOXYRIBONUCLEIC ACID BY NEOCARZINOSTATIN, AUROMOMYCIN, AND BLEOMYCIN: STUDIES ON BASE RELEASE AND NUCLEOTIDE SEQUENCE SPECIFICITY.

Takeshita M, Kappen LS, Grollman AP, Eisenberg M, Goldberg IH
Dept. Pharmacological Sciences, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Biochemistry; 20(26):7599-7606 1981

The nucleotide sequence specificity of neocarzinostatin (NCS), auromomycin (AUR), bleomycin (Blm), phleomycin (Phlm), and tallysomycin (Tlm) has been determined by using these antibiotics and their associated chromophores to create strand scissions in end-labeled restriction fragments of DNA and then determining the base sequence of the oligonucleotides formed. NCS and the NCS chromophore induce similar patterns of cleavage in DNA fragments labeled at the 5' terminus. The pattern produced by the AUR chromophore also resembles that of its holoantibiotic. Dithiothreitol enhances the rate of cleavage of DNA by the AUR chromophore but does not alter the sequence specificity. The results suggest that the polypeptide component of AUR and NCS serves primarily as a carrier for the chromophore. When tested with a fragment labeled at the 3' terminus, the products of NCS and AUR cleavage do not display the patterns of chemically produced oligonucleotides cleaved at phosphodiester bonds, suggesting that the 5' terminus is modified by a sugar fragment. NCS primarily attacks thymine (75% of the total bases attacked) and, to a lesser extent, adenine (19%) and cytosine (6%). AUR preferentially attacks guanine (67% of total bases), while attacking less often thymine (24%) and adenine (9%). Bleomycin and its analogues preferentially cleave purine-pyrimidine (5' to 3') and pyrimidine-pyrimidine (3' to 5') sequences. All (5' to 3') GT and GC sequences were cleaved. Phlm G and Phlm-Pep are less active than bleomycin toward purines while Tlm was more active. The patterns of cleavage produced by Blm A2 and Glm B6 are similar, while those produced by Phlm-Pep, Phlm G, Blm-B1', and Blm-Pep resemble one another. The cleavage pattern of Tlm shows quantitative differences from the other analogues tested. Differences between bleomycin and its analogues may be related to structural differences in these molecules. (Author abstract) (36 Refs)

7. ANTHRAMYCIN BINDING TO DEOXYRIBONUCLEIC ACID-MITOMYCIN C COMPLEXES. EVIDENCE FOR DRUG-INDUCED DEOXYRIBONUCLEIC ACID CONFORMATIONAL CHANGE AND COOPERATIVITY IN MITOMYCIN C BIN DING.

Kaplan DJ, Hurley LH
(c/o Hurley) Drug Dynamics Inst., Coll. Pharmacy, Univ. Texas at Austin, Austin, TX, 78712
Biochemistry; 20(26):7572-7580 1981

Anthramycin and mitomycin C (MC) are two DNA reactive drugs, which bind covalently to GC pairs producing different effects on DNA: anthramycin stiffening and MC distortion. This paper describes experiments in which we have used anthramycin as a probe to sense quantitatively the effects on DNA of MC binding. Saturation binding experiments show that both anthramycin and MC partially inhibit the binding of the other drug to DNA (maximum inhibition by MC and anthramycin, 22.4% and 19.7%, respectively) but by a mechanism other than direct site exclusion. This suggests that MC binds in the major groove of DNA, since anthramycin is known to bind in the minor groove. An abrupt reduction in the binding of anthramycin to DNA-MC complexes occurs between MC binding ratios of 0.030 and 0.035, which parallels and probably results from sudden intensification of a MC-induced DNA conformational change occurring between these binding ratios. Dialysis measurements indicate that anthramycin is very possibly binding at sites distant from MC sites and suggest a clustering of closely bound MC chromophores resulting from possible cooperative binding. S1 nuclease digest experiments demonstrate an initial enhancement of nuclease activity in DNA-MC complexes, the magnitude of which correlates well with the reduction of anthramycin binding, relative to the degree of MC binding. The enhanced nuclease activity in these complexes indicates regions of exposed DNA or helix base distortion which is related to or is the result of conformational change. (Author abstract) (43 Refs)

8. EFFECT OF DEOXYRIBONUCLEIC ACID ON THE PRODUCTION OF REDUCED OXYGEN BY BLEOMYCIN AND IRON.

Caspary WJ, Lanzo DA, Niziak C
Cellular and Genetic Toxicology Branch, NCI/National Toxicology Program, NIH, Bethesda, MD, 20205
Biochemistry; 21(2):334-338 1982

The binding of bleomycin to DNA in the presence and absence of ferric iron was measured by fluorescence spectroscopy. In millimolar concentrations of tris(hydroxymethyl)aminomethane, pH 7.5, approx 80% of the bleomycin binds to DNA. Ferric iron seems to have significant effect on the binding of DNA to bleomycin. The induction of oxygen uptake by ferrous iron and bleomycin was monitored in the presence and absence of DNA. DNA has no effect on the rate of oxygen uptake. Therefore, the iron binding site and the DNA binding site appear to be independent of each other. Under conditions where 80% of the bleomycin is bound to DNA, the ferrous iron-bleomycin-induced reduction of oxygen follows Michaelis-Menten kinetics. Ferrous iron autoxidation produces ethylene from methional. The addition of bleomycin greatly increases ethylene production. DNA, under conditions where 80% of the bleomycin is bound to DNA, inhibits ethylene production. Since ethylene is a measure of hydroxyl radical production, we conclude that DNA is able to compete with methional for the hydroxyl radical. We postulate a mechanism for DNA double-strand breaks in which the bleomycin selectively binds to DNA and recurrently produces the hydroxyl radical at that site. The localized generation of many hydroxyl radicals as provided by the proposed oxidation-reduction cycle mechanism may cause multiple strand breaks taking place on both strands of the DNA duplex leading to double-strand breaks. Since catalase, but not superoxide dismutase, is able to inhibit ferrous iron-bleomycin-induced products of the hydroxyl radical, hydrogen peroxide, but not the superoxide radical, is the immediate precursor of the hydroxyl radical. (Author abstract) (43 Refs)

9. VARIATIONS IN CHROMOSOME NUMBERS AND THEIR POSSIBLE RELATIONSHIP TO THE DEVELOPMENT OF 8-AZAGUANINE RESISTANCE IN V79 CHINESE HAMSTER CELLS.

Fox M, Radacic M

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Cell Biol Int Rep; 6(1):39-48 1982

Evidence is presented for breakdown of heteroploid V-79 cells both during growth in 8-azaguanine and after removal of cells from selective pressure. Results suggest that acquired during effects at autosomal loci controlling either catabolic enzymes of the purine synthetic pathway or a dominant suppressor of hypoxanthine-guanine-phosphoribosyl-transferase activity. (18 Refs)

10. A COMPARATIVE ASSESSMENT OF THE IN VITRO EFFECTS OF DRUGS ON CELLS BY MEANS OF COLONY ASSAYS OR FLOW MICROFLUORIMETRY.

Hill BT, Whelan RD, Rupniak T, Dennis LY, Rosholt HT

Lab. Cellular Chemotherapy, Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London WC2A 3PX, England

Cancer Chemother Pharmacol; 7(1):21-26 1981

The use of flow microfluorimetric (FMC) analysis for drug sensitivity testing is reported. This procedure provides results within a few hr and allows a study of the kinetic effects of drugs on cells. In 24 hr drug exposures logarithmically growing murine neuroblastoma cells were treated with a range of concentrations of various antitumor drugs and their colony-forming ability was assessed. Depending on the drug used, survival curves had plateaus at as high a level as 50%, eg, with methotrexate (MTX), or at as low a level as 20%, eg with VM-26. Cell kill was consistently less after 1 hr exposures, even at increased drug concentrations. FMC analysis of 24 hr treated cells at lower drug concentrations (80% survival) showed noticeable arrest accumulation (1) at the G1/S boundary for 2,4-diamino-5-(3',4'-dichlorophenyl)-6-methyl pyrimidine (DDMP), 5-fluorouracil, MTX, and dramatically, hydroxyurea; (2) at the G2/M phases with melphalan, peptichemio, adriamycin, dibromodulcitol, bleomycin, razoxane, vincristine, and vindesine, and only slightly with cis-platinum; and (3) additionally in the S phase with dibromodulcitol, peptichemio, and melphalan. Higher drug concentrations (40% survival) of DDMP, 5-fluorouracil, MTX, or hydroxyurea resulted in a loss of G2/M populations. Melphalan, peptichemio, and cis-platinum all resulted in a pronounced accumulation of cells in the G2 and/or M phases where a block and/or cell kill has probably occurred. Substantial G1 populations, however, remained. Arrest was almost totally in the G2/M phases with a loss of both G1 and S phase cells after treatment with vincristine, vindesine, VM-26, VP-16-213, and razoxane. Treatment with adriamycin, bleomycin, and dibromodulcitol at these high dose levels resulted in a broad accumulation of most cells shifted away from G1 into S and G2/M phases. (22 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

11. EFFECT OF ESTRADIOL ON THE ULTRASTRUCTURE OF THE MCF7 HUMAN BREAST CANCER CELLS IN CULTURE.

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Cancer Res; 42(2):667-673 1982

We have analyzed the effect of estradiol and of two classes of antiestrogens on the morphology of the MCF7 human breast cancer cell line by scanning and transmission electron microscopy. Estradiol progressively increased the number and the length of microvilli at the cell surface. The density of the microvilli network increased between 2 and 11 days of estrogen treatment, while the cells became more globular and less tightly attached to the surface of the dish. Estradiol also progressively transformed cells into secretory cells containing, at Day 2, large, clear mitochondria and, at Day 4, rough endoplasmic reticulum and Golgi complexes. At Day 6, secretory granules (diameter, 0.2 um), which mainly contained glycoproteins, were first observed in the cytoplasm. By Day 8, they were concentrated at the cell membrane and being liberated into the medium. Larger granules (diameter, 0.8 um), which probably contained lipids, were observed later (Day 11). Cell cultures in 10% fetal calf serum not treated by charcoal contained secretory granules. The modifications were induced by physiological concentrations of estradiol but not 5alpha-dihydrotestosterone. Progesterone (10 nM for 8 days) completely inhibited the effect of estradiol on the microvilli and secretory activity. Tamoxifen or hydroxytamoxifen did not induce secretory activity but did alter the cell morphology compared to control cells. The effects of estradiol were observed in other estrogen receptor-positive breast cancer cell lines (ZR 75-1, T 47 D) but not in an estrogen receptor-negative cell line (BT 2 0). This morphological evidence that estrogens modify the cell surface of breast cancer cells in culture and transform them into 'secretory cells' complements evidence that they induce the release of a glycoprotein with a mol wt of approx 50,000 into the culture medium. (The mol wt was found first to be 46,000. It seems to be closer to 52,000 in a 10% polyacrylamide gel and by using the NEN-labeled proteins as mol wt markers.) (Author abstract) (30 Refs)

12. INHIBITION OF THYMIDYLATE SYNTHASE BY HYDROXYUREA IN RAPIDLY PROLIFERATING P815 MASTOCYTOMA CELLS.

Boehm TL, Kreis W, Drahovsky D
Zentrum der Biologischen Chemie, Universitat Frankfurt am Main, D-6000 Frankfurt/Main, W. Germany
Biochim Biophys Acta; 696(1):52-56 1982

The incorporation of [14C]deoxycytidine, [3H]deoxyuridine, and [3H]thymidine, respectively into pyrimidine bases of DNA has been measured in rapidly proliferating P815 mouse mastocytoma cells in the presence of hydroxyurea. The incorporation of [14C]deoxycytidine-derived radioactivity into DNA cytosines is increased when compared to the incorporation into DNA thymines. The [3H]deoxyuridine-derived radioactivity is incorporated solely into DNA thymines and this incorporation is inhibited by hydroxyurea in a dose-dependent manner. This suggests an inhibitory effect of hydroxyurea on the thymidylate synthase which was proved in experiments in which the conversion of deoxyuridine monophosphate into deoxythymidine monophosphate catalyzed by a crude enzyme preparation from P815 cells was inhibited in the presence of hydroxyurea. Enzymatic DNA methylation as measured by the conversion of incorporated [14C]deoxycytidine into 5-methylcytosines was not affected by hydroxyurea. (Author abstract) (10 Refs)

13. VINCRISTINE INHIBITS THE SYNTHESIS OF MALONDIALDEHYDE BY HUMAN PLATELETS IN VITRO.

Martin JF, Greaves M

Univ. Dept. Medicine, Floor M, The Royal Hallamshire Hosp., Glossop Road, Sheffield S10 2JF, England

Cancer; 49(4):665-668 1982

When platelet-rich plasma was preincubated with vincristine, a depression in malondialdehyde production was seen when compared with saline controls. Colchicine caused an increase in malondialdehyde production. If prostaglandins are important in tumor-cell metabolism, then vincristine might exert some of its cytotoxic effect by depressing prostaglandin production. (Author abstract) (19 Refs)

14. REGULATION OF CELL DIVISION IN A HUMAN GLIOMA CELL CLONE BY ARACHIDONIC ACID AND ALPHA-TOCOPHEROLQUINONE.

Liepkalns VA, Liepkalns CI, Cornwell DG

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Cancer Lett; 15(2):173-178 1982

Lipid peroxidation and cell proliferation were examined in a human glioma cell clone (12-18 CV) cultured with a polyunsaturated fatty acid and the antioxidant alpha-tocopherolquinone (TPQ). Lipid peroxidation, as measured by the thiobarbituric acid test, was retained by both confluent and proliferating tumor cells when incubated with either 8,11,14-eicosatrienoic acid or arachidonic acid. TPQ (10 uM) inhibited polyunsaturated fatty acid peroxidation. Exogenous arachidonic acid inhibited cell proliferation in a dose-dependent manner and its effect was blocked by TPQ. Diminished fatty acid release from neoplastic brain tissue may limit availability of polyunsaturated fatty acids for lipid peroxidation and the modulation of cell proliferation that may occur through this process. (14 Refs)

15. BIOCHEMICAL ACTIVATION OF AZQ [3,6-DIAZIRIDINYL-2,5-BIS(CARBOETHOXYAMINO)-1,4 BENZOQUINONE] TO ITS FREE RADICAL SPECIES.

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Cancer Treat Rep; 66(2):339-342 1982

The aziridinyl quinone 3,6-diaziridinyl-2,5-bis(carboethoxyamino)-1,4 benzoquinone is an antitumor agent that enhances electron flow from reduced nicotinamide adenine dinucleotide phosphate (NADPH) to molecular oxygen in rat liver microsomes, rat liver nuclei, and purified NADPH-cytochrome C reductase. The process is enzymatic and has an optimum pH of 7.5; NADPH is the preferred cofactor. Electron spin resonance studies show the presence of a free radical semiquinone characterized by five hyperfine lines at g = 2.0046. (Author abstract) (8 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

16. EFFECT OF CAFFEINE ON CELL KILLING, MUTATION INDUCTION, DNA REPAIR, AND DNA SYNTHESIS AFTER TREATMENT WITH ETHYLNITROSOUREA.

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Carcinogenesis; 2(12):1267-1271 1981

The effect of caffeine on cell killing, mutation induction, DNA repair, and inhibition of DNA synthesis was investigated in a clonal derivative of M3-1 Chinese hamster cells after treatment with N-ethyl-N-nitrosourea (ENU). Caffeine enhanced cell killing but had no effect on the mutation frequency of viable cells for the two genetic markers, 6-thioguanine resistance and ouabain resistance. The removal of ethylated purine bases from DNA was as follows: most of the 3-ethyladenine was lost in 20 hr (greater than 85%) and approx 45% of the 7-ethylguanine was lost in 45 hr, whereas 75-93% of the O6-ethylguanine was still present at this time. Caffeine did not seen to influence these rates significantly. The ENU-induced inhibition of DNA synthesis was reversed by caffeine. It is concluded that the potentiation of ENU-induced cell killing by caffeine is caused by the increased frequency of DNA replication past damaged sites in parental DNA. (Author abstract) (25 Refs)

17. ISOLATION AND PROPERTIES OF CHINESE HAMSTER LUNG CELLS RESISTANT TO ELLIPTICINE DERIVATIVES.

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Cancer Treat Rep; 66(2):327-338 1982

Chinese hamster lung cells resistant to 9-OH-ellipticine (9-OH-E) were selected in vitro by adding stepwise increasing drug concentrations to the cell growth medium. This selection procedure resulted in the isolation of two sublines, about 10-fold and 12-fold resistant to 9-OH-E. This level of resistance did not increase even after about 30 months of drug exposure. Cytogenetic studies revealed that the resistant cells carry several discrete karyotype modifications, the most striking being the absence of one No. 5 chromosome and the presence of a marker chromosome characterized by peculiar G-banding. Development of 9-OH-E resistance was also associated with some changes in cell properties such as modifications of morphology and growth parameters, lower oncogenic potential, and cross-resistance to a variety of antitumor agents. Although these results suggest that the resistance is associated with a modification of cell membrane properties, drug uptake studies did not show any significant difference between the parental sensitive cells and the resistant sublines. (Author abstract) (36 Refs)

18. ENHANCEMENT OF METHOTREXATE ANTI-CANCER THERAPY BY ALTERATION OF METHYL GROUP NUTRITION IN MICE BEARING L1210 (MEETING ABSTRACT).

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Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

This study is to determine whether the efficacy and safety of Methotrexate (MTX) can be enhanced by two measures, either separately or together, namely, use of 5-methyltetradhydrofolate (MF, the normal plasma folate) for 'rescue' and administration of methionine in BDF1 mice bearing L1210 lymphosarcoma. In these preliminary studies 200 L1210 cells were implanted sc, MTX administered sc, 54 hr later and any 'rescue' administered 15 hr later again. MF or Leucovorin (CF) were given sc at 100 mg/kg. Methionine was injected ip at 5 or 25 mg/mouse. MTX doses were 0, 63, 125, 250 or 500 mg/kg. Mice were scored for survival and tumors. Without therapy, mice died from tumors at approximately 15 days whereas toxic deaths were before day 12. In 'rescue' regimens, survival rates after MF were equivalent to those after CF. To test if MF would selectively rescue normal tissues rather than cancer tissues, MF were administered simultaneously with MTX; survival rates were identical to no therapy controls, inferior to use of MTX alone. In 'rescue' regimens, the administration of methionine simultaneously with the MF or CF enhanced efficacy without affecting toxicity. When MTX was administered without MF or CF, the administration of methionine had little effect. (no Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

19. EFFECTS OF ARABINOSYL CYTOSINE AND 5-AZACYTIDINE ON THE INTESTINAL ABSORPTION OF NUTRIENTS.

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Toxicol Appl Pharmacol; 62(1):73-80 1982

The effects of two pyrimidine antimetabolites, arabinosyl cytosine (ara-C) and 5-azacytidine (5-aza-C), on the intestinal transport of glucose, amino acids, and electrolytes were studied. The everted sac technique was used. A marked decrease in D-glucose, 3-O-methyl-D-glucose, and L-tyrosine transport was noted. Results suggest that active metabolites of ara-C and 5-aza-C are involved in inhibitory effects on intestinal absorption; the inhibition may be a contributing factor in the malnutrition and diarrhea commonly associated with administration of these anticancer drugs. (22 Refs)

20. CROSS RESISTANCE AND CELLULAR UPTAKE OF 4'-O-METHYLDOXORUBICIN IN EXPERIMENTAL TUMORS WITH ACQUIRED RESISTANCE TO DOXORUBICIN.

Di Marco A, Skovsgaard T, Casazza AM, Pratesi G, Nissen NI, Dano K

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Cancer Chemother Pharmacol; 7(1):15-20 1981

Activity of 4-O-methyldoxorubicin (MDR) against lines of Ehrlich and P388 ascites tumors in which resistance to doxorubicin (DOX) was acquired after treatment with the drug was investigated. Results of in vitro studies of cellular uptake of MDR are reported. At their optimal doses, both MDR and DOX achieved significant and pronounced prolongation of median survival time of mice inoculated with wild-type P388 leukemia cells. No differences between the drugs were noted. When given at the optimal dose for inhibiting wild type P388 cells, both drugs had only a slight effect on the survival of mice inoculated with the DOX-resistant subline, P388/DX+. At drug doses approaching the LD10 the antitumor activity of MDR was comparable to that of DOX in wild type Ehrlich ascites tumor-inoculated mice, whereas no activity could be demonstrated against a similar tumor line selected for resistance to DOX. This line was thus cross-resistant to MDR. Inhibition of energy metabolism increased the steady-state uptake of MDR in resistant Ehrlich ascites tumor cells. This uptake was decreased again by restoration of energy metabolism. Thus, there is probably increased extrusion of MDR from DOX-resistant cells. (8 Refs)

21. TRIAZENE METABOLISM. I. THE EFFECT OF SUBSTITUENTS IN THE ARYL GROUP ON THE KINETICS OF ENZYME-CATALYSED N-DEMETHYLATION OF 1-ARYL-3,3-DIMETHYLTRIAZENES.

Godin JR, Vaughan K, Renton KW

Dept. Chemistry, Saint Mary's Univ., Halifax, N.S. B3H 3C3, Canada

Can J Physiol Pharmacol; 59(12):1234-1238 1981

A series of antitumor dimethylarytriazenes (ArN = N-NMe2) have been studied with respect to enzyme catalyzed N-demethylation by liver microsomes and the Km values determined by Lineweaver-Burk treatment. The substituent in the aryl group of the triazene does not significantly effect the magnitude of Km, which is of the same order of magnitude as the Km for aminopyrine. On the other hand, dimethyltriazenes appear to have lower Km values for demethylation than the structurally similar dimethylnitrosamines. Monomethyltriazenes, the proposed active metabolites of the dimethyltriazenes, do not undergo appreciable demethylation in the presence of microsomes and it appears that the dimethyltriazenes only demethylate once during metabolism. Spontaneous formaldehyde release from the hydroxymethyltriazene in the presence of the Nash reagent prevented an analogous study of the metabolism of these compounds. (Author abstract) (27 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

22. ADRIAMYCIN ANALOGUES. PREPARATION AND ANTITUMOR EVALUATION OF 7-O-(BETA-D-GLUCOSAMINYL)DAUNOMYCINONE AND 7-O-(BETA-D-GLUCOSAMINYL)ADRIAMYCINONE AND THEIR N-TRIFLUOROACETYL DERIVATIVES.

Israel M, Murray RJ
Div. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
J Med Chem; 25(1):24-28 1982

The title compounds were prepared by Koenigs-Knorr condensation of 3,4,6-tri-O-acetyl-2-deoxy-2[(trifluoroacetyl)amino] alpha-D-glucopyranosyl bromide with daunomycinone or a side-chain protected adriamycinone, followed by selective hydrolysis of blocking groups. Despite poor complexation with DNA and weak growth-inhibitory properties in vitro, the glucosaminyl analogues of the antitumor antibiotics daunorubicin and adriamycin, at their optimal (highest nontoxic) doses, exhibited antileukemic activity equivalent to that of adriamycin against a usually drug-refractory mouse leukemia model system (L1210) in vivo. These findings, together with other data from these laboratories, continue to support the hypothesis that the mechanism of action of adriamycin and related agents cannot be due exclusively to DNA binding, as has earlier been believed. (Author abstract) (30 Refs)

23. ENHANCED ANTITUMOR PROPERTIES OF 3'-(4-MORPHOLINYL) AND 3'-(4-METHOXY-1-PIPERIDINYL) DERIVATIVES OF 3'-DEAMINODAUNORUBICIN.

Mosher CW, Wu HY, Fujiwara AN, Acton EM
Bio-Organic Chemistry Lab., Life Sciences Div., SRI International, Menlo Park, CA, 94025
J Med Chem; 25(1):18-24 1982

Reductive N,N-dialkylation of daunorubicin with 2,2'-oxydiacetaldehyde and NaBH3CN occurred in two steps without interruption and with cyclization to form 3'-(4-morpholonyl)-3'-deaminodaunorubicin. This derivative retained the antitumor efficacy of doxorubicin against mouse leukemia P388 but at one-fortieth the dose; hence, it is the most potent anthracycline analogue synthesized so far. The 4-methoxy-1-piperidinyl derivative, similarly prepared with 3-methoxygluytaraldehyde, showed improved efficacy against p388, though at normal doses. Results with a series of analogues indicate that incorporation of the N in the new ring and the presence of an ether O at the 4-position are critical for enhanced activity. (Author abstract) (19 Refs)

EFFECTS OF ANTIMETASTATIC AGENTS

24. ANTIMETASTATIC EFFECTS AND TUMOR PROTEINASE INHIBITION BY SPLEEN INTRACELLULAR INHIBITORS OF NEUTRAL PROTEINASES.

Giraldi T, Sava G, Kopitar M, Brzin J, Suhar A, Turk V
Istituto di Farmacologia, Universita di Trieste, I-34100 Trieste, Italy
Eur J Cancer Clin Oncol; 17(12):1301-1306 1981

The mechanism of the antimetastatic effects of spleen intracellular inhibitors of neutral proteinases (SNPI's) has been examined in mice bearing subcutaneous Lewis lung carcinoma. SNPI-1 and SNPI-2 selectively depress the formation of spontaneous lung metastasis. A dose-dependent inhibition of the proteolytic activity of subcutaneous primary tumor homogenate at neutral pH was observed after ip administration of SNPI-1; its selective antimetastatic effects were evident only at the lower dosage used. This finding indicates that the administration of SNPI's, in spite of causing a dose-dependent depression of tumor proteinases, which presumably participate in the early phases of the process of metastasis formation, may also exert other actions, reducing their antimetastatic effects. (Author abstract) (46 Refs)

25. THE ROLE OF GLYCOCONJUGATES IN METASTATIC MELANOMA BLOOD-BORNE ARREST AND CELL SURFACE PROPERTIES.

Irimura T, Nicolson GL
Dept. Tumor Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
J Supramol Struct Cell Biochem; 17(4):325-336 1981

The role of glycoconjugates in cell-surface and blood-borne implantation (BBI) properties of murine melanoma cells (MMC) were studied. MMC of lines B16-F1 (which has low BBI potential) and B16F10 (which has high BBI potential) were exposed in vitro to tunicamycin (0.5 ug/ml for 36 hr), which prevents glycosylation of glycoproteins by inhibiting formation of lipid-linked oligosaccharide precursors. Modification of cell-surface glycoproteins was examined by measuring the decrease in binding by sialogalactoproteins of 125I-labeled Ricinus communis agglutinin I. Treatment with tunicamycin reduced protein synthesis in B16-F10 cells by 50% and reduced DNA synthesis and growth rates in both MMC strains. Tunicamycin reduced BBI in the lungs of C57BL/6 mice receiving iv injections of MMC, without an apparent shift to extrapulmonary sites. Electron microscopic examination showed that B16-F1 and B16-F10 cells treated with tunicamycin developed morphologic changes, including rounding of the cells and formation of numerous surface blebs. Treatment with tunicamycin reduced in vitro adhesion of MMC to endothelial cell monolayers, endothelial basal lamina, and polyvinyl-immobilized fibronectin. Results suggest that tunicamycin reduces experimental metastasis of murine melanoma by modifying surface glycoproteins that determine the adhesive properties of MMC. (62 Refs)

26. INHIBITION OF TUMOR VASCULARIZATION BY TRANEXAMIC ACID. EXPERIMENTAL STUDIES ON POSSIBLE MECHANISMS.

Sundbeck A, Karlsson L, Lilja J, Peterson HI
Lab. Biorheology, Dept. Surgery I, Univ. Goteborg, Sahlgrenska Sjukhuset, Goteborg, Sweden
Anticancer Res; 1(5):299-304 1981

The influence of tranexamic acid (TA) and indomethacin (IM) on tumor growth (TG) rate was studied. Drugs were administered either during early or late TG to determine the time of maximal effect on TG. Sarcoma induced with 20-methylcholanthrene was transplanted im into inbred rats from a Lister strain. A large number of vascular connections (VC) was found between the tumor and muscle vascular beds. Reduction of VC between tumor and surrounding muscle with a comparatively sharp border between the two tissues was found in animals given TA. Similar observations were made in animals given IM. Electron microscopy revealed small vessels in control tumors and tumors from animals given TA. Some of the vessels were surrounded by a single sheet of smooth muscle cells. In some vessels an invasion of tumor cells into the lumen was observed. No obvious differences were seen between control tumors and tumors from animals treated with TA. No differences in the general ultrastructural appearance between control and TA tumors were found. Growth rate of tumors was significantly reduced by both TA and IM administered early or late during TG. An explanation for the inhibition of TG and vascularization by TA and IM may be reduction of a local inflamatory reaction induced by tumor transplantation and stimulating tumor vascularization. (14 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

27. ADRIAMYCIN ANALOGUES. NOVEL ANOMERIC RIBOFURANOSIDE ANALOGUES OF DAUNORUBICIN.

Israel M, Airey JE, Murray RJ, Gillard JW
Div. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
J Med Chem; 25(1):28-31 1982

The synthesis, cell growth-inhibitory activity, in vivo antileukemic activity, and extent of DNA binding of the alpha- and beta-anomeric 7-O-(3-amino-3,5-dideoxy-D-ribofuranosyl)daunomycinones and their trifluoroacetamides are described. These compounds are unique in that they are the first reported furanoside analogues of the antitumor antibiotics daunorubicin and adriamycin. Continuing analysis of structure-activity relationships amongst natural and semisynthetic anthracyclines fails to reveal a predictable relationship between in vivo antitumor activity and the in vitro properties of DNA complexation and cell growth inhibition. (Author abstract) (27 Refs)

28. RNA BREAKAGE ACTIVITY OF THE METHANOL EXTRACT OF AUROMOMYCIN.

Kalvin DM, Huang CH, Lischwe MA, Peters EH, Prestayko AW, Crooke ST
816 Tappan, apt. 10, Ann Arbor, MI, 48104
Cancer Chemother Pharmacol; 7(1):41-50 1981

Components of the antitumor antibiotic auromomycin (AM) were characterized. An AM preparation (AM0) was extracted using methanol. Absorption studies indicated that the extract (AMX) contained 70% of the non-peptide chromophore contained in AM0; the residue (AMR) contained 20% of the chromophore. AMX contained 21-26% of the peptides in AM0. AMX exhibited 121% +-28% of the capacity (DDC) of AM0 to degrade PM-2 DNA. AMR exhibited 22% +-3.8% of the DDC of AM0. A mixture of AMX and AMR had a DDC 78% +-6.7% less than that of AM0. AMX showed a DDC against single-stranded DNA 6.5x that against double-stranded DNA, as indicated by agarose gel electrophoresis. Differences in total DDC of AM0, AMX, AMR, and AMX + AMR were attributed to possible interactions between peptides and the non-peptide chromophore in the AM0 and the mixture of AMX and AMR. Fractionation of AMX by means of Sephadex chromatography produced several fractions showing DDC that contained enriched non-peptide chromophore relative to peptides. Exposure of AMX to UV radiation eliminated DDC. Results indicate that DDC of AM is due to the non-peptide chromophore component. (24 Refs)

INTERFERON AND OTHER ANTIVIRALS

29. PLATELET-DERIVED GROWTH FACTOR (PDGF) ENHANCES THE GROWTH OF MOLONEY SARCOMA VIRUS-INDUCED TUMORS IN MICE.

Inglot AD, Inglot O
Lab. Tumor Virology, Dept. Tumor Immunology, Inst. Immunology and Experimental Therapy, Polish Acad. Sciences, Czerska 12, 53-114 Wroclaw, Poland
Arch Immunol Ther Exp (Warsz); 29(4):431-437 1981

The intramuscular (im) administration of bovine or human platelet derived growth factor (PDGF) had a marked potentiating effect on the growth of Moloney sarcoma virus (MSV)-induced tumors in BALB/c mice. PDGF had the tumor-promoting-activity when administered im on the side of inoculation of MSV 2 days after the virus, and subsequently every 2nd day for 2-3 wk. The extent of MSV-induced tumor promoting activity of PDGF was age and sex-related. In view of the recently described antagonism in action between growth factors and interferons it is suggested that both families of hormones play an important role in controlling the neoplastic proliferation. (Author abstract) (16 Refs)

30. NATURAL CYTOTOXICITY TO MURINE CYTOMEGALOVIRUS-INFECTED CELLS MEDIATED BY MOUSE LYMPHOID CELLS: ROLE OF INTERFERON IN THE ENDOGENOUS NATURAL CYTOTOXICITY REACTION.

Lee GD, Keller R
Dept. Microbiology, Michael Reese Hosp. and Medical Center, Chicago, IL, 60616
Infect Immun; 35(1):5-12 1982

Lymphoid cells from unstimulated normal C57BL/6J mice were shown to lyse murine cytomegalovirus (MCMV)-infected syngeneic mouse embryo fibroblasts but not uninfected mouse embryo fibroblasts. This cytotoxicity by mouse effector cells was not restricted to MCMV-infected syngeneic cells. The effector cells mediating this cytotoxicity against MCMV-infected cells are similar to described natural killer (NK) cells mediating lysis of tumor cells and virus-infected cells. Because of the described augmentation of NK activity by interferon, we examined the role of interferon in the NK reaction. Although low levels of virus-induced interferon were detectable in supernatants of MCMV-infected mouse embryo fibroblasts, no interferon was detectable in supernatants of MCMV-infected rat heart fibroblasts, a target significantly more sensitive to NK cytolysis than infected mouse embryo fibroblasts. We were able to augment the NK reaction against MCMV-infected cells by in vitro treatments with interferon. The amounts of interferon required for augmentation were significantly greater than the amounts generated by infected target cells. In vitro interferon-stimulated NK cells retained selective cytotoxic activity since they continued to remain incapable of lysing uninfected target cells. MCMV-infected rat heart fibroblasts induced more interferon and were also more susceptible to NK activity than MCMV-infected mouse embryo fibroblasts. In spite of this difference in interferon-inducing capacity, there was no augmentation of cytotoxicity of MCMV-infected mouse embryo fibroblasts when mouse splenocytes were cocultivated with both target cells. Finally, when production of interferon in the NK reaction was inhibited by the addition of actinomycin D, no reduction of NK activity was seen. Our findings suggest that native mouse NK cells can discriminate between MCMV-infected cells and uninfected cells, this ability leading to the selective lysis of the virus-infected cells. Furthermore, although we could demonstrate augmentation of NK activity by interferon, interferon activation of NK cells may not be a necessary precondition for the development of endogenous NK activity. (35 Refs)

31. PRODUCTION OF HUMAN LYMPHOBLASTOID INTERFERON WITH NAMALWA CELLS. I. PRODUCTION OF INTERFERON WITH STATIONARY CULTURE METHOD.

Ding Z, Zhang Y, Chang Z, Zhang B, Gu P
Natl. Vaccine and Serum Inst., Beijing, People's Republic of China
Zhonghua Weishengwuxue He Mianyixue Zazh; 1(2):90-94 1981

Although interferon has shown promise in cancer therapy, its large-scale production is the problem that prevents an extensive use. A method for a potential large-scale production of human interferon, based on lymphoblastoid Namalwa cell line, is presented. When passaged at a 1:10 split ratio and cultured for 5 days, cell count reached 2 x 10(6) cells/ml, which can be split again. During cell cultivation, it was essential to maintain pH at 6.4-7.0 and to insure an adequate supply of oxygen to achieve food results. When Namalwa cells reached 3-5 x 10(6) cells/ml, the cell suspension was induced with 10-200 HAU/ml of the virus strain NDV-F, at 35-36 C for 22-24 hr; and at end of this period the supernatant was collected by centrifugation. After adjusting its pH to 2.0 with HCl and left at 4-8 C for 5 days to kill residual virus the interferon titer was usually 4.0-5.0 log10 units/ml. Higher interferon yields were obtained when fresher virus and more active cells were used. (13 Refs) (In CHI)

32. REVERSAL BY HYPOTONIC MEDIUM OF THE ANTIVIRAL STATE INDUCED BY LYMPHOBLASTOID INTERFERON IN HUMAN HELA CELLS.

Munoz A, Carrasco L
(c/o Carrasco) Dept. Microbiology, Centro de Biologia Molecular, Universidad Autonoma, Canto Blanco, Madrid 34, Spain
Intervirology; 16(2):106-113 1981

The induction kinetics of the antiviral state in HeLa cells treated with human lymphoblastoid interferon (IFN) was studied. In cells treated with 4-200 U/ml IFN, the antiviral state was fully established in 7-9 hr. Inhibition of virus multiplication was more rapid if the concentration of IFN was increased to 1,000 U/ml. This antiviral state gradually disappeared during the 48 hr after IFN removal. Several compounds known to act on the cell membrane or on the cytoskeleton were tested for their influence on the establishment and reversal of the antiviral state. None of them were found to influence these two parameters to a significant extent. In contrast, placing HeLa cells in medium lacking NaCl partially reversed the blockade to virus multiplication induced by IFN treatment. Cells treated with IFN and later placed in hypotonic medium synthesized virus proteins after encephalomyocarditis virus infection, although at a reduced level compared to cells that had not been treated with IFN. (Author abstract) (13 Refs)

33. STIMULATION BY INTERFERON OF INDUCTION OF DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIA CELLS.

Tomida M, Yamamoto Y, Hozumi M
Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan
Biochem Biophys Res Commun; 104(1):30-37 1982

The effects of purified human leukocyte interferon-alpha (IFA) and partially purified fibroblast interferon-beta (IFB) on induction of differentiation of human promyelocytic leukemia cells (HL-60) into granulocytes and macrophages were studied. HL-60 cells maintained for 6 days in conditioned medium of mouse myeloid leukemia M1 cells with phytohemagglutinin were induced to differentiate predominantly into monocytes and macrophages (M+Ms) in a concentration-dependent manner in concentrations up to 50% (vol/vol) of the conditioned medium. The interferons alone neither inhibited HL-60 cell growth nor induced differentiation, but both enhanced growth inhibition and induction of differentiation into M+Ms by suboptimal concentrations the conditioned medium of M1 cells. The interferons also increased macrophage inducing power of low concentrations of 12-O-tetradecanoylphorbol-13-acetate and the granulocyte inducing effect of retinoic acid. The mechanism of IFA and IFB action is not known, but it seems to differ from that of cerebrospinal fluid. (27 Refs)

34. COMPLEMENTATION BETWEEN PHOSPHONOACETIC ACID-RESISTANT AND -SENSITIVE VARIANTS OF HERPES SIMPLEX VIRUSES: EVIDENCE FOR AN OLIGOMERIC PROTEIN WITH RESTRICTED INTRACELLULAR DIFFUSION AS THE DETERMINANT OF RESISTANCE AND SENSITIVITY.

Honess RW

Div. Virology, Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England

J Gen Virol; 57(part2):297-306 1981

Complementation between phosphonoacetic acid (PAA)-resistant (Pr) and -sensitive (Ps) variants of herpes simplex virus Type 1 (HSV-1) and Type 2 (HSV-2) was studied to provide information on the function of the virus-coded DNA polymerase. Complementation within and between serotypes was demonstrated, with the growth of the Ps partner in mixed infections becoming relatively more resistant and the Pr partner relatively more sensitive to PAA than in the corresponding single infections. However, the relative contribution of the Ps partner to the mixed infection had a disproportionately large effect on the resultant sensitivity of the mixed infection which was incompatible with non-interactive (eg monomeric) polymerase molecules as determinants of PAA sensitivity and resistance. Although a number of solutions gave equally good fits to the available data, the simplest was obtained by assuming that the functional DNA polymerase was a trimer and that only the (Pr)(3) homotrimer was active in the presence of the drug. In addition, yields from mixed infections in the presence of PAA were enriched for the resistant partner relative to yields in the absence of the drug. These latter results suggested that the intracellular distribution of resistant DNA polymerase oligomers was non-random with respect to resistant and sensitive template genomes and these resistant polymerase molecules were more likely to encounter and replicate resistant than sensitive genomes. Such an explantation seems to require vectorial nuclear-cytoplasm-nucleus translocation and restricted diffusion of transcript and gene products determining resistance. (Author abstract) (19 Refs)

35. EFFECT OF PROTEASE INHIBITORS ON THE ACTIVATION OF EPSTEIN-BARR VIRUS REPRESSED IN CULTURED LYMPHOID CELLS.

Morigaki T, Sugawara K, Ito Y
(c/o Ito) Dept. Micribiology, Faculty of Medicine, Kyoto Univ., Kyoto 606, Japan
Intervirology; 16(1):49-52 1981

The effects of five microbial and one synthetic protease inhibitor on the activation of Epstein-Barr virus expression in latently infected lymphoblastoid cells were studied. All protease inhibitors tested suppressed both viral antigen induction by 5-iododeoxyuridine treatment and cell growth in general. Among the inhibitors, however, antipain and pepstatin exerted a relatively strong and significant suppressive effect on antigen induction as compared to their inhibitory effect on cell growth. (Author abstract) (11 Refs)

OTHER RELATED STUDIES

36. HYPERTHERMIA: A NEW APPROACH TO THE TREATMENT OF CANCER.

Sculier JP, Klastersky J
Inst. Jules Bordet, Centre des Tumeurs, Universite Libre de Bruxelles, 1, rue Heger-Bordet, 1000 Bruxelles, Belgium
Nouv Presse Med; 10(42):3487-3490 1981

Hyperthermia has been known since the last century to be effective against cancer, but it has only developed into a new therapeutic method during the past 20 yr. The authors review the theoretical and experimental backgrounds of fever therapy and discuss its local and general applications currently under study, including possible synergistic effects with radiotherapy and/or chemotherapy. Particular attention is paid to systemic hyperthermia. (Author abstract) (20 Refs) (In FRE)

37. VITAMIN B6 AND CANCER (REVIEW).

Tryfiates GP, Morris HP, Sonidis GP

Dept. Biochemistry, West Virginia Univ. Sch. Medicine, Morgantown, WV, 26506

Anticancer Res; 1(5):263-267 1981

Effects of vitamin B6 (comprised of pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives) on tumor growth are reviewed, particularly with respect to transplantable minimum deviation Morris hepatomas. When dietary pyridoxine was restricted, tumor growth was inhibited and enzyme activity was altered, especially in the presence of growing hepatomas. Supplementation of the diet with vitamin B6 stimulates tumor growth, shortens survival time of mice, and prevents and increase in the survival time of the tumor-bearing animals which were treated with 5-fluorouracil. Pyridoxine restriction appears to affect both transhydroxymethylase and synthetase by different mechanisms which synergistically augment tumor growth inhibition. When the vitamin complexing agent L-penicillamine (L-PEN) was injected into Buffalo rats bearing No 777 Morris hepatomas, vitamin B6 was inactivated in situ, and the animals became energetic and were able to care for themselves within 4 days. L-PEN forms a stable complex with pyridoxal 5'-phosphate in vivo and/or in vitro resulting in decreased aminotransferase activity levels. Even at advanced tumor stages, inactivation of vitamin B6 in situ can be highly beneficial for the host. (34 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. ACCUMULATION OF S PHASE POPULATIONS OF FM3A CELLS GROWING IN THE MOUSE DUE TO ADMINISTRATION OF 5-FLUORO-2'-DEOXYURIDINE.

Hanaoka F, Nagata K, Watanabe Y, Enomoto T, Yamada M
Dept. Physiological Chemistry, Faculty Pharmaceutical Sciences, Univ. Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan
Cell Struct Funct; 6(4):357-365 1981

Procedures and results of administration of 5-fluoro-2'-deoxyuridine (FudR) to mouse FM3A cells growing in the mouse peritoneal cavity are described. A single administration of 100 ug FUdR caused the accumulation of 70-80% of FM3A cells in the S phase; indirect evidence suggests that most of the cells were at the G1/S boundary. The cytoplasmic fraction of mouse FM3A cells contained a very high level of the P-1 fraction of DNA polymerase alpha, and the DNA polymerase alpha in nuclear extract from FUdR-treated cells was about 3x as active as that from the randomly-growing cells. (14 Refs)

2. CIS AND TRANS-DIAMMINEDICHLOROPLATINUM(II) BINDING PRODUCES DIFFERENT TERTIARY STRUCTURAL CHANGES ON SV40 DNA.

Scovell WM, Kroos LR
Dept. Chemistry, Bowling Green State Univ., Bowling Green, OH, 43403
Biochem Biophys Res Commun; 104(4):1597-1603 1982

Tertiary structural changes produced by cis-diamminedichloroplatinum(II) (cisDDP) and trans-diamminedichloroplatinum(II) (trans-DDP) binding on simian virus 40 (SV40) DNA was studied by gel electrophoresis, assuming that the mobility of the DNA is proportional to the absolute number of supercoils. The Pt bound to DNA was determined by atomic absorption spectrophotometry after unbound Pt was separated by drop dialysis. Cis-DDP binding unwinds the supercoiled DNA to the intact relaxed form in about 6 hr, which is about 4x faster than observed for trans-DDP. When the SV40 DNA is incubated with the isomers for up to 30 min, cis-DDP reduces the mobility of supercoiled DNA at very short reaction times, an effect produced with trans-DDP only after an interval 50x longer. Results suggest that the cis-isomer exhibits a mode of binding different than that of the trans-isomer, a mode which is responsible for the more effective unwinding of the DNA. (29 Refs)

3. THE RELATIONSHIP BETWEEN DNA AND CHROMOSOME DAMAGE AFTER BLEOMYCIN TREATMENT: DOSE-RESPONSE MEASUREMENTS.

Sognier MA, Hittelman WN, Pollard M
Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Mutat Res; 93(1):149-159 1982

Formation of chromosomal aberrations (CA) was studied in Chinese hamster ovary cells exposed to bleomycin in various concentrations and for various exposure times. Curves of alkaline elution of DNA and CA (as measured by G2 premature condensation of chromosomes) showed a two-compartment response with a more sensitive compartment at low doses. The two-compartment response was less evident when CA was enumerated in mitotic figures, suggesting that cellular chromatin determines sensitivity to bleomycin. Use of different doses and times to produce equivalent DNA damage indicated that rapidly repaired DNA lesions are not involved in chromatid exchanges. (24 Refs)

4. IRON(II)-BLEOMYCIN. BIOCHEMICAL AND SPECTRAL PROPERTIES IN THE PRESENCE OF RADICAL SCAVENGERS.

Rodriguez LO, Hecht SM
Dept. Chemistry, Univ. Virginia, Charlottesville, VA, 22901
Biochem Biophys Res Commun; 104(4):1470-1476 1982

The effect of hydroxyl free and dioxygen free radical scavengers on the ability of Fe(II)-bleomycin (Fe(II)-BLM) to degrade radiolabeled PM-2 DNA was studied by the release of (3H)thymine. Dimethylsulfoxide (DMSO) completely suppressed the degradation of DNA by Fenton's reagent and H_2O_2. The damage mediated by bleomycin A2 in the presence of Fe(II) was not affected by the same amount of DMSO. The release of (3H)thymine from radiolabeled PM-2 DNA by 2.5 uM bleomycin was the same in the presence or absence of 80 milliM t-butyl phenylnitrone (BPN). As anticipated, DNA degradation by Fenton's reagent was completely suppressed by this BPN treatment. The scavenger tetrakis(4-N-methylpyridyl)porphineiron(III) was without effect as an inhibitor of DNA degradation. Corroborative evidence was also obtained by study of the intensity of the epr (electron paramagnetic resonance) signal produced by Fe(II)-BLM in the presence of BPN, compared to that produced by an equimolar amount of Fe(II) and excess H_2O_2. It is concluded that the fragmentation of DNA produced by Fe(II)-BLM is not due to either hydroxyl free or dioxygen free radicals. It is suggested that DNA degradation is initiated by an 'active complex' consisting of BLM, metal and oxygen that functions by abstracting free H from susceptible sites on DNA. (31 Refs)

5. COMPARISON OF THE SEQUENCES AT SPECIFIC SITES ON DNA CLEAVED BY THE ANTITUMOR ANTIBIOTICS TALISOMYCIN AND BLEOMYCIN.

Mirabelli CK, Beattie WG, Huang CH, Prestayko AW, Crooke ST
Bristol-Baylor Lab., Dept. Pharmacology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77131
Cancer Res; 42(4):1399-1404 1982

We have investigated the site-specific cleavage of DNA by the antitumor antibiotics talisomycin and bleomycin by using 5'- or 3'-terminal 32P-labeled restriction fragments of pBR.322 DNA. Both drugs cleaved DNA preferentially at G-C and G-T sequences. However, the relative amounts of cleavage at particular cleavage sites differed between talisomysin and bleomycin at concentrations of the drugs which produced similar extents of total cleavage. In addition, talisomycin produced specific cleavages at G-A sequences which were relatively resistant to cleavage by bleomycin. Within a preferred sequence group (ie, G-C sequences), some sites were cleaved to a greater extent relative to others by both talisomycin and bleomycin, suggesting that a greater degree of specificity than that provided by only two nucleotides is involved in the site-specific recognition and cleavage of DNA by these drugs. (Author abstract) (29 Refs)

6. PRELIMINARY CHARACTERIZATION OF THE ADDUCTS FORMED BETWEEN THE ANTITUMOR COMPOUND CIS-PT(NH3)2CL2 AND DNA.

Johnson NP
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, Centre National de la Recherche Scientifique, 205 route de Narbonne, 31400 Toulouse, France
Biochem Biophys Res Commun; 104(4):1394-1400 1982

Electrophoresis of the products formed by the reaction of cis-Pt(NH3)2Cl2 (cP) with DNA gave a profile of Pt concentration which contained five peaks whose relative intensity varied with the amount of cP fixed on the DNA. Similar study with two Pt compounds which lacked antitumor activity showed a different manner of binding to DNA. DNA isolated from Escherichia coli which had been treated with cP or [Pt(dien)Cl]Cl did not yield the same profiles on electrophoresis as the corresponding Pt-DNA compounds formed in vitro. (10 Refs)

7. COMPARATIVE STUDIES OF DNA CROSS-LINKING AND CYTOTOXICITY IN BURKITT'S LYMPHOMA CELL LINES TREATED WITH CIS-DIAMMINEDICHLOROPLATINUM(II) AND L-PHENYLALANINE MUSTARD.

Ducore JM, Erickson LC, Zwelling LA, Laurent G, Kohn KW
Dept. Pediatrics, Univ. Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX, 75235
Cancer Res; 42(3):897-902 1982

Three Burkitt's lymphoma cell lines were studied for their response to cis-diamminedichloroplatinum(II) (cis-DDP) and L-phenylalanine mustard (L-PAM) with the objective of relating cytotoxicity to DNA cross-linking in human cells. Cytotoxicity was measured by cell proliferation and colony formation assays. DNA interstrand and DNA-protein cross-linking were measured by alkaline elution. Two of the cell lines showed quantitative agreement between cytotoxicity and DNA cross-linking assays following treatment with cis-DDP or L-PAM. The correlation with DNA-protein cross-linking was not as good as with interstrand cross-linking. With the third cell line, cytotoxicity and interstrand cross-linking were correlated in response to L-PAM but not in response to cis-DDP. When this line was treated with cis-DDP, cross-linking was low, but cytotoxicity was high. This line differed from the other two lines in that, following treatment with either cis-DDP or L-PAM, substantial cell lysis or disruption occurred 12 to 14 hr following treatment. The results are consistent with a general correlation between DNA cross-linking and cytotoxicity in human cells treated with bifunctional agents. An exceptional cell type, however, is described which appears to have a reduced tolerance to certain types of DNA damage, the reduced tolerance being expressed by early cell lysis or disruption. (Author abstract) (19 Refs)

8. ELEVATED LEVEL OF ENZYMATIC DNA METHYLATION IN CELLS TREATED WITH 1-BETA-D-ARABINOFURANOSYLCYTOSINE.

Boehm TL, Drahovsky D
(c/o Drahovsky) Zentrum der Biologischen Chemie, Universitat Frankfurt, Theodor Stern-Kai 7, D-6000 Frankfurt am Main 70, W. Germany
Cancer Res; 42(4):1537-1540 1982

When mouse P815 mastocytoma cells are cultured in the presence of 1-beta-D-arabinofuranosylcytosine (ara-C), a dose-dependent inhibition of cell proliferation and DNA synthesis can be observed. The DNA synthesized in the presence of ara-C is more highly enzymatically methylated than that of controls as measured by conversion of incorporated [14C]deoxycytidine-derived radioactivity into 5-methylcytosines. Analysis of DNAs by means of the bacterial restriction enzyme HpaII and its isoschizomer MspI revealed an aberrant DNA methylation pattern after ara-C treatment. The hypermethylation of DNA persisted also in the cell cycle following the treatment in the absence of ara-C. No such changes in DNA methylation patterns following ara-C treatment were observed in P815/ara-C, a subclone of P815 cells resistant to ara-C. (Author abstract) (22 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

9. EFFECT OF CYTOSTATICS ON THE MIGRATION OF LEUKOCYTES.

Horvath M, Bakacs T

Natl. Inst. Oncology, PO Box 21.1525, Budapest, Hungary

Oncology; 39(1):29-30 1982

The effect of chemotherapeutic agents - cytosine arabinoside, methotrexate, procarbazine, vinblastine and vincristine - generally applied in the treatment of human cancer were tested on the motility of polymorphonuclear leukocytes. In the concentrations applied, cytosine arabinoside and procarbazine were inhibitory, vincristine had no effect, methotrexate and vinblastine stimulated the migration at lower concentrations. (Author abstract) (6 Refs)

10. COMBINED EFFECTS OF VINBLASTINE AND VINCRISTINE ON MOUSE HEPATOCYTES WITH RESPECT TO ULTRASTRUCTURAL ELEMENTS.

Rassat J, Robenek H, Themann H

Medizinische Cytobiologie, Westring 3, D - 4400 Munster, W. Germany

Exp Pathol; 20(3):163-174 1981

The results of a single dose of the microtubule-destroying agents vinblastine/vincristine (0.5 mg/0.5 mg) on the ultrastructural elements of mouse hepatocytes was studied using the techniques of thin-sectioning and freeze-fracture following intravenous injection of the drugs. Several cytoplasmic modifications were observed in the hepatocytes. These included the storage of lipid droplets, a heavy accumulation of autophagosomes and vacuoles with very low density lipoprotein (VLDL)-like vesicles, large glycogen fields and dilated intercellular spaces with intrahepatocytic vacuoles. The rough endoplasmic reticulum exhibited pathological changes with loss of ribosomes and the bile canaliculi exhibited in some cases the loss of microvilli as well as dilatation of the lumen. The tight junctions surrounding the bile canaliculi exhibited alterations as well. The strands were reduced in number and showed a less organized arrangement . The gap junctions showed an increase in size as well as an irregular outline in contrast to controls. These findings are interpreted as non-specific toxic phenomena. However, the possibility cannot be precluded that certain phenomena, such as alterations in the cell junctions, may be attributable to specific microtubule-destroying properties of the drugs. (Author abstract) (61 Refs)

11. EFFECT OF VINBLASTINE, VINCRISTINE, AND VINDESINE ON NEUTROPHIL PHAGOCYTOSIS AND IODINATION.

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Cancer Treat Rep; 66(3):505-508 1982

The ability of neutrophils to phagocytose Saccharomyces cerevisiae and iodinate Staphylococcus aureus and Candida albicans was evaluated when the neutrophils were incubated with therapeutic and above-therapeutic concentrations of vinblastine, vincristine, or vindesine. The phagocytic capacity, but not the phagocytic rate, was decreased in the presence of vincristine but not the other drugs. Above-therapeutic concentrations of vinblastine and vincristine reduced the iodination of C albicans when compared with the control. We concluded that therapeutic doses of these drugs were not detrimental to important neutrophil functions. (Author abstract) (13 Refs)

12. ADENYLATE CYCLASE SYSTEM IN CELLS OF EHRLICH ASCITES CARCINOMA SENSITIVE AND RESISTANT TO 5-FLUOROURACIL.

Shlemkevich MP, Iurkiv VA, Melikhov VI
Medical Inst., Lvov, USSR
Ukr Biokhim Zh; 54(1):76-79 1982

Activity of adenylate cyclase (AC) was studied in Ehrlich ascites carcinoma cells resistant and sensitive to 5-fluorouracil. Resistant cells had higher AC activity and lower phosphodiesterase activity than sensitive cells. The content of cyclic adenylate in resistant cells was significantly higher than that in the sensitive cells. Sodium fluoride increased AC activity both in resistant and sensitive cells. Prostaglandin E2 did not affect AC activity in sensitive cells and produced a 2x increase of AC activity in resistant cells. (11 Refs) (In RUS)

13. TRIMETHOPRIM-INDUCED AUGMENTATION OF HUMAN NATURAL KILLER ACTIVITY IN VITRO.

Matheson DS, Wilson RW, Green B
Faculty Medicine, Dept. Pediatrics, Univ. Calgary, Health Science Centre Room 1875, Calgary, Alberta T2N 4N1, Canada
Immunopharmacology; 4(1):73-77 1982

Effects of trimethoprim-sulfamethoxazole (TMP-SMX) on the natural killer (NK) activity of peripheral blood mononuclear cells from normal humans were studied in vitro. TMP-SMX consistently caused an augmentation in NK activity, and did not alter the background lysis of the target cells in the absence of effector cells. Augmentation by TMP alone essentially paralleled that of TMP-SMX, suggesting that TMP was the drug which mediated the response. (12 Refs)

14. THE EFFECT OF HARRINGTONINE AND AND ITS ALLIED ALKALOIDS ON THE INCORPORATION OF LABELED AMINO ACIDS INTO PROTEINS OF CELLS OF TRANSPLANTABLE LEUKEMIAS L-615 AND P-388.

Xu Y, Du C, Zhang F, Ji X
Inst. Materia Medica, Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Yaoxue Xuebao; 16(9):661-666 1981

Effects of four different harringtonines (harringtonine, homoharringtone, isoharringtonin, and deoxyharringtonine) on protein biosynthesis in experimental leukemias (L-615 and P388) are described. Tests for the effects consisted of the incorporation of tritium-labeled DL-leucine and L-asparagine and of carbon-14-labeled DL-phenylalanine into proteins of mouse leukemia P388 ascitic cells and L-615 splenic tissue. When 1/5 of the LD50 of any one of the alkaloids was injected ip or iv into mice bearing the leukemias, marked inhibition of protein synthesis was observed. The effects were rapid, with max inhibition observed 30 min to 4 hr after administration of the drug; recovery occurred after 24 hr. The alkaloids had similar time-effect curves. The significance of these results in relation to chemotherapy of leukemia is discussed. (17 Refs) (In CHI)

15. RECENT CONCEPTS ON THE MECHANISM OF ACTION OF METHOTREXATE.

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Cancer Treat Rep; 65(Suppl1):3-12 1981

The mechanism of action of methotrexate (MTX) is discussed in relation to blockage of dihydrofolate reductase (DHFR). Blockage of DHFR prevents regeneration of tetrahydrofolate (H4folate) produced from dihydrofolate (H2folate) produced in the de novo synthesis of thymidylate from uridylate, with the result that H4folate cofactors cease to operate. Free intracellular MTX is required for inhibition of H4folate synthesis. The biochemical basis of the requirement for free MTX is discussed in relation to the following parameters: interaction among MTX, H2folate, and DHFR within the target cell; model studies in a cell-free system on effects of H2folate on MTX binding to DHFR; and computer analysis of the interactions among MTX, H2folate, and DHFR. Cytotoxic determinants of MTX are described: membrane transport, DHFR level, DHFR inhibitor constant for MTX, basal rate of de novo thymidylate synthesis and effects of fluoropyrimidines, and synthesis of polyglutamyl derivatives of MTX. The rationale for use of high-dose MTX regimens is discussed. (25 Refs)

16. THE BINDING OF PLATINUM ETHYLENEDIAMINE DICHLORIDE TO PROTEINS, IN VITRO AND IN VIVO.

Robins AB
Dept. Radiopharmacology, Inst. Cancer Res., Sutton, Surrey, England
Chem Biol Interact; 38(3):349-356 1982

The binding to proteins of platinum ethylenediamine dichloride (PtenCl2) labeled with carbon-14 has been studied in vitro and in vivo. The metal complex binds to proteins in plasma with a half-time of about 1 hr and is distributed over all protein classes. At pharmacologically relevant levels the binding of platinum does not affect the biological function of the protein, eg, the immunoglobulins. Although the in vitro toxicity of PtenCl2 is decreased by binding to the proteins of the culture medium, it has not yet proved possible to determine whether binding in vivo, eg to tumor cytosol proteins, leads to loss in toxicity and whether it is reversible. (Author abstract) (15 Refs)

17. FURTHER STUDIES ON ADRIAMYCIN INDUCED IN VITRO LIPID PEROXIDATION.

Facchinetti T, Muh-Zange M, Salmona M, Carini M, Remmer H
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Chem Biol Interact; 38(3):357-367 1982

Adriamycin (AM)-induced lipid peroxidation was studied in rat liver microsomal system, measuring color produced by thiobarbituric acid (TBA) reactive material and the development of volatile hydrocarbons. The onset of this degradative process is closely related to the AM content. This phenomenon appears to be highly influenced by the buffer used for the microsomal preparation. The effect of AM on Fe-ADP-induced lipid peroxidation in liver microsomes has also been studied. (Author abstract) (17 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

18. CONTROL OF IN VIVO (CELLULAR) PHLEOMYCIN SENSITIVITY BY NUCLEAR GENOTYPE, GROWTH PHASE, AND METAL IONS.

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Cancer Res; 42(3):929-933 1982

Nuclear genotype, growth phase, and the presence of metal ions all proved to be important in controlling the lethal effects of phleomycin in eukaryotic Saccharomyces cerevisiae. Among 120 normal and radiation-sensitive strains compared for their sensitivities to lethal effects of phleomycin, all mutant strains exhibiting enhanced sensitivities to phleomycin killing were also sensitive to killing by ionizing radiation. Mutants exhibiting sensitivities to phleomycin similar to normal strains of the same ploidy were sensitive to ultraviolet radiation. We conclude that cellular recovery from phleomycin-induced damage in yeast depends upon the function of some or all of 13 independent genes and upon at least some of the same steps in cellular pathways for the biological repair of damage by ionizing radiation. In this respect, the action of phleomycin is similar to the action of its structurally similar analog, bleomycin, even though phleomycin was substantially more cytotoxic. Stationary-phase haploid yeast cells were more sensitive than exponentially growing cells to killing by phleomycin. Survival of stationary-phase yeast was reduced to 0.3 -0.07% (S.E.) after 20-min exposures to phleomycin (1 ug/ml; approx 6.7 x 10(-7) M), but lethal effects of phleomycin were completely eradicated (98% survival) by the presence of 0.05 M ethylenediaminetetraacetate during the treatment period. The inactivation indicates an important role for one or more metal ion(s) in the in vivo toxicity of the phleomycin-bleomycin group of anticancer antibiotics. (Author abstract) (46 Refs)

19. EFFECTS OF DOPAMINE AGONISTS AND ANTAGONISTS ON MURINE MELANOMA: CORRELATION WITH DOPAMINE BINDING ACTIVITY.

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Cancer; 49(6):1178-1184 1982

The biosynthetic pathway producing melanin is present in many melanomas. Previous investigations have suggested that pharmacologic levels of intermediates in this pathway (L-dopa, dopamine, and their analogues) may inhibit macromolecular synthesis in some tissue culture melanoma cell lines and prolong survival in tumor-bearing mice. Recently, a potent antidopamine drug (pimozide) has been developed. This study was designed to investigate the effects of these drugs on murine melanomas and to correlate effect on macromolecular synthesis with competitive dopamine binding activity (receptors) and melanin synthesis. Three murine melanomas (F1, F10, B16) were studied. The amelanotic B16 cell line showed no inhibition by dopa, dopamine, or pimozide when assayed for 14C-leu or 3H-TdR incorporation. Using a competitive binding assay, only low levels of dopamine binding were present. The very melanotic F1 cell line showed no inhibition by dopa or dopamine, but pimozide inhibited 14C-leu and 3H-TdR incorporation in a dose-response fashion; 50% inhibition was noted at 10(-9) M concentration with no loss in cell viability as tested by trypan blue exclusion or cell counting. Competitive dopamine binding was present (19 pmoles per g of wet tissue) with a Kd of 0.2 nM, figures approximating those seen in normal dog caudate nucleus controls. The F10 line, with melanin production between the B16 and F1, was intermediate in terms of inhibition of 14C-leu and 3H-TdR incorporation and dopamine binding. Purified melanin did not bind and, thus, does not appear to explain these binding results. These data suggest that pimozide, a drug which is a potent dopamine antagonist, may inhibit 14C-leu and 3H-TdR incorporation in murine melanoma cells and that competitive dopamine binding (receptor) appears to correlate with this inhibition. This drug and the dopamine binding assay may be useful in the study of human melanoma. (Author abstract) (15 Refs)

20. AMPHOTERICIN B AND THE BLOOD-BRAIN BARRIER TO METHOTREXATE.

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Neurosurgery; 10(2):224-226 1982

The effect of iv amphotericin B (AMP) on the blood-brain-barrier (BBB) permeability to methotrexate (MTX) was studied in male Wistar rats. AMP was infused iv for 20 min to a total dose of 1 mg/kg body wt and BB permeability to 3H-MTX, 24Na, and 36Cl- was examined. Permeability-surface area (PS) products for the compounds in treated and control animals were not significantly different: for MTX the PS value was approx 2.8 x 10(-5) cubic cm/g/sec. The PS product for 36Cl- increased slightly but not significantly. No significant differences in mean arterial pressure or blood gases were noted in treated animals compared with controls. The results demonstrate that AMP has no significant effect on BBB permeability to the three molecules. A possible explanation is that AMP acts on the luminal membrane of the capillary endothelium but cannot reach the abluminal membrane. Substances can then pass from blood to endothelial cell but not from endothelial cell to brain. The small increase in 36Cl- permeability may reflect the exchange of Cl- by the K pump on the abluminal membrane that removes K from the brain. AMP may be useful in enhancing the antitumor effect of chemotherapeutic agents when given intrathecally. (22 Refs)

21. THE ROLE OF METHOTREXATE AND DIHYDROFOLATE POLYGLUTAMATES IN THE ENHANCEMENT OF FLUOROURACIL ACTION BY METHOTREXATE.

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Cancer Treat Rep; 65(Suppl1):29-35 1981

The effect of the methotrexate (MTX)-5-fluorouracil (FUra) combination on L1210 cell viability was highly sequence dependent in that a 1.4 log (25-fold) increase in cytotoxicity was observed when the MTX exposure preceded FUra, as compared to the reverse sequence. The formation of ternary complexes of thymidylate synthetase has been examined as a basis for the interaction of FUra and MTX in L1210 cells. L1210 cells converted 39% of the total intracellular MTX into MTX-poly-gamma-glutamates within 4 hr of a 1 uM MTX exposure. MTX-diglutamate (2,4-diamino,N(10)-methylpteroyldiglutamate) and MTX-triglutamate were the predominant metabolites. In contrast to the ternary complexes formed with MTX and MTX-diglutamate, the 5-fluorodeoxyuridylate (FdUMP)-7,8-dihydropteroylpentaglutamate-enzyme and the FdUMP-5,10-methylenetetrahydropteroylpentaglutamate enzyme and the FdUMP-5,10-methylenetetrahydropteroylpentaglutamate enzyme complexes were stable to polyacrylamide gel electrophoresis under nondenaturing conditions. MTX-diglutamate enhanced the extent of tight-binding inhibition of thymidylate synthetase activity by FdUMP in the presence of saturating 5,10-methylenetetrahydropteroylpentaglutamate, suggesting that MTX-diglutamate did not antagonize the formation of FdUMP-5,10-methylenetetrahydropteroylpentaglutamate enzyme complex. We propose that the sequence-dependent effect of MTX plus FUra on L1210 cell viability results from MTX and MTX polyglutamate inhibition of dihydrofolate reductase, and consequently a trapping of intracellular folates as dihydrofolate polyglutamates that could increase the extent of FdUMP binding to thymidylate synthetase. (Author abstract) (24 Refs)

22. THE EFFECTS OF INHIBITORS OF DNA BIOSYNTHESIS ON THE CYTOTOXICITY OF 6-THIOGUANINE.

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Cancer Biochem Biophys; 5(3):189-194 1981

The effects of hydroxyurea, 1-beta-D-arabinofuranosylcytosine, and 5-fluorodeoxyuridine on the antiproliferative activity of 6-thioguanine (6-TG) in exponentially growing L1210 leukemia cell cultures were measured by changes in (methyl-3H)thymidine, (U-3H)uridine, and (8-14C)adenine incorporation. None of the inhibitors of DNA biosynthesis caused additive toxicity when used with 6-TG but instead significantly decreased the delayed cytotoxicity of 6-TG, suggesting that cell injury caused by the agent is mediated at least in part through DNA synthetic processes. Cells exposed to 10 uM 6-TG for 30 min in G1/S or S phases of the cell cycle were considerably more susceptible to the cytotoxic action of 6-TG than those treated in G2 phase. However, some cytotoxicity was also evident after exposure in G2 phase, suggesting that multiple biochemical lesions account for the effects. Alkaline sucrose gradient sedimentation of L1210 cells exposed to 6-TG revealed that the purine analogue causes structural breaks in DNA. (35 Refs)

23. COMPARATIVE MISONIDAZOLE METABOLISM IN ANAEROBIC BACTERIA AND HYPOXIC CHINESE HAMSTER LUNG FIBROBLAST (V-79-473) CELLS.

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Biochem Pharmacol; 31(3):411-414 1982

The metabolism of the radiation sensitizer misonidazole was similar in anaerobic cecal contents and hypoxic Chinese hamster lung fibroblasts (V-79-473). Both systems formed the amino derivative of misonidazole, [1-(2-aminoimidazol-1-yl)-3-methoxypropan-2-ol] (AIM), and urea, as well as a metabolite, (2-hydroxy-3-methoxypropyl)-guanidine (G), which has not been described previously. It appears that the nitro group of misonidazole was reduced to form AIM and that this compound was then hydrolyzed to yield either urea or G, the latter in yields of 25% (tissue culture) to 55% (cecal contents). When tested with the Ames tester strain, both G and AIM were slightly mutagenic only for strain TA 98 and then only in the presence of the system for microsomal activation. (Author abstract) (11 Refs)

24. DECREASED CYTOTOXICITY OF CIS-DIAMMINEDICHLOROPLATINUM(II) BY ALPHA-DIFLUOROMETHYLORNITHINE DEPLETION OF POLYAMINES IN 9L RAT BRAIN TUMOR CELLS IN VITRO.

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Cancer Res; 42(4):1296-1299 1982

Before treatment with the cytotoxic drug cis-dichlorodiammineplatinum(II) (cis-platinum), 9L rat brain gliosarcoma cells grown in vitro were depleted of intracellular polyamines by alpha-difluoromethylornithine (DFMO; 10 mM, 48 hr), an enzyme-activated, irreversible inhibitor of the polyamine-synthetic enzyme ornithine decarboxylase. In contrast to studies that showed that the cytotoxicity of 1,3-bis (2-chloroethyl)-1-nitrosourea as measured by colony-forming efficiency is enhanced by DFMO depletion of intracellular polyamines, the cytotoxicity of cis-platinum was significantly decreased in polyamine-depleted 9L cells. At 10, 1, and 0.1% survival levels the dose modification factors were 2.0 to 2.1. Addition of exogenous putrescine to polyamine-depleted 9L cells 24 hr before treatment with cis-platinum partially reversed this phenomenon. When 9L cells were treated either with DFMO and cis-platinum or with DFMO, putrescine, and cis-platinum for 1 hr, a time period that is too short for DFMO to affect intracellular polyamine levels, the cytotoxicity of cis-platinum was decreased, but to a significantly lesser extent than by the 48 hr DFMO pretreatment. Putrescine alone did not alter the cytotoxic effect of cis-platinum when administered either 24 or 1 hr before treatment. DFMO appears to affect cis-platinum cytotoxicity by two different mechanisms, the first mediated through polyamine depletion and the second through a direct interaction with cis-platinum. (Author abstract) (29 Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

25. BIOCHEMICAL CORRELATES OF RESPONSIVENESS AND COLLATERAL SENSITIVITY OF SOME METHOTREXATE-RESISTANT MURINE TUMORS TO THE LIPOPHILIC ANTIFOLATE, METOPRINE.

Sirotnak FM, Moccio DM, Goutas LJ, Kelleher LE, Montgomery JA
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cancer Res; 42(3):924-928 1982

The M5076 murine 'ovarian' tumor which is naturally refractive to methotrexate was found to be highly responsive to the lipophilic antifolate, metroprine. M5076 cells were markedly deficient in mediated entry of methotrexate. This was in contrast to the L1210 leukemia, a tumor highly responsive to methotrexate but poorly responsive to metoprine. Two L1210 leukemia sublines, with acquired resistance to methotrexate by virtue of a deficiency in mediated entry of drug similar to that seen for M5076 cells, were found to be collaterally sensitive to metoprine. The insensitivity to methotrexate of the M5076 tumor and the two L1210 sublines is associated with low saturability (high Km) and reduced capacity (low Vmax) for mediated influx of drug. 5-Methyltetrahydrofolate, the major circulating folate in blood but not metoprine, shares this mediated route for entry. Therefore, a relatively low level of accumulation of this natural folate in these methotrexate-resistant tumors, in the face of a metoprine-induced blockade at the level of dihydrofolate reductase, probably accounts for the high sensitivity of these tumors to this lipophilic agent. Evidence for this notion was derived during transport and growth experiments in vitro using 5-formyltetrahydrofolate as a model folate coenzyme. The value of influx Vmax of this folate compound in a transport-deficient methotrexate-resistant subline compared to the parental L1210 was reduced to the same extent as that shown for methotrexate. Growth of this resistant L1210 subline showed a greater requirement for this model compound than did the parental line. Also, the concentration necessary for 50% inhibition by metoprine in the presence of this reduced folate was lower in the resistant subline. Inhibition of each cell line by metoprine, on the other hand, was the same when folic acid was used as the folate source. The implications of these findings for the use of lipophilic antifolates as alternative therapy for some methotrexate-resistant tumors are discussed. (Author abstract) (26 Refs)

26. COMPARISON OF LYMPHATIC UPTAKE, METABOLISM, EXCRETION, AND BIODISTRIBUTION OF FREE AND LIPOSOME-ENTRAPPED [14C]CYTOSINE BETA-D-ARABINOFURANOSIDE FOLLOWING INTRAPERITONEAL ADMINISTRATION TO RATS.

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Drug Metab Dispos; 10(1):40-46 1982

Free [14C]cytosine beta-D-arabinofuranoside ([14C]ara-C) was completely absorbed from the peritoneal cavity of thoracic duct-cannulated rats by 6 hr after ip dosing. 14C levels in most tissues were higher at 4 hr than at 12 hr after dosing and were generally undetectable at 24 hr. By 6 hr after treatment only 2% of the dose was recovered in lymph, whereas 90% had been excreted in urine. Liposome entrapment of ara-C reduced the rates at which the drug was absorbed from the peritoneal cavity and excreted in urine while enhancing lymphatic uptake of the drug by more than 10-fold. Radioactivity in plasma and most tissues achieved higher concentrations and persisted for longer periods in rats given liposome-entrapped ara-C than in rats receiving the free drug. Most striking was the localization of 14C-activity in renal and thoracic lymph nodes of rats given liposome-entrapped ara-C, with 300 to 1,000-fold higher levels present at 4, 12, and 24 hr after dosing than in corresponding lymph nodes of rats receiving the free drug. The metabolic conversion of ara-C to uracil beta-D-arabinofuranoside (ara-U) was reduced by approximately three-fold following liposome entrapment of the drug. The enhanced lymphatic uptake and the localization and persistance of ara-C in lymph nodes resulting from liposome entrapment of the drug may be of benefit in treating tumors that metastasize via lymphatic pathways. (Author abstract) (46 Refs)

27. IDENTIFICATION OF THE PRINCIPAL BILIARY METABOLITE OF 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE IN RATS.

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Drug Metab Dispos; 10(1):35-39 1982

m-AMSA [4'-(9-acridinylamino)methanesulfon-m-anisidide] labeled in either the acridine or anilino portion was used to investigate the disposition of this antitumor agent in rats. The principal biliary metabolite, which accounts for approximately 80% of the total biliary radioactivity for 90 min after administration and greater than 50% of the administered dose by 180 min after administration, had both the acridine and the anilino portions intact. Isolation and purification of the principal metabolite was achieved by preparative thin-layer chromatography on silica gel and column chromatography on Amberlite XAD-2 resin. A nuclear magnetic resonance (NMR) spectrum of the DCI salt in D2O showed that the metabolite is the m-AMSA-glutathione conjugate in which the thioether linkage occurs at the 5'-position of the anilino ring. Synthesis of the metabolite was achieved by oxidizing m-AMSA with active MnO2 to -methanesulfonyl- -(9-acridinyl)-3'-methoxy-2',5'-cyclohexadiene-1',4' diimine (m-AQDI) followed by reaction of m-AQDI with glutathione. The 1H-NMR spectrum of the synthetic product proved identical with that of the isolated metabolite. The demonstration that the principal biliary metabolite of m-AMSA involves glutathione bound to the 9-anilino ring suggests that m-AMSA may be bioactivated in vivo to the quinoidal diimine, m-AQDI. (Author abstract) (15 Refs)

28. NEW ANTITUMOR IMIDAZOLE DERIVATIVE, 5-CARBAMOYL-1H-IMIDAZOL-4-YL PIPERONYLATE, AS AN INHIBITOR OF PURINE SYNTHESIS AND ITS ACTIVATION BY ADENINE PHOSPHORIBOSYLTRANSFERASE.

Fukui M, Inaba M, Tsukagoshi S, Sakurai Y
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Cancer Res; 42(3):1098-1102 1982

The mechanism of action of 5-carbamoyl-1H-imidazol-4-yl piperonylate (SL-1250) which has a broad antitumor spectrum, was examined by in vitro cell culture and enzymatic studies. In the serum-containing culture medium, SL-1250 was rapidly deacylated to 4-carbamoylimidazolium 5-olate (SM-108). Thus, SL-1250 might be acting on the cells in the form of SM-108. The growth of L5178Y cells was completely inhibited by 10(-5) M SL-1250. It should be noted that this growth inhibition was significantly reversed in the presence of equimolar concentrations of guanine, guanosine, or guanosine 5'-monophosphate to those of SL-1250. However, hypoxanthine and xanthine were not effective. These effects of purine addition were observed to be quite similar in growth inhibition by SM-108. It was found that inosine 5'-monophosphate dehydrogenase (EC 1.2.1.14; IMP dehydrogenase), a key enzyme of de novo purine synthesis, from Ehrlich carcinoma cells was inhibited by SM-108 only when 5-phospho-alpha-D-ribose 1-diphosphate (PRPP) and MgCl2 coexisted with SM-108. In contrast, a chemically synthetic ribonucleotide of SM-108 inhibited IMP dehydrogenase without PRPP and MgCl2, and the mode of inhibition was competitive with the Ki value of 2 x 10(-8) M. On the other hand, the inhibition of either growth of L5178Y cells or IMP dehydrogenase in the presence of PRPP and MgCl2 by these compounds was reversed by adenine. A nucleotide of

SM-108 was chromatographically identified when [14C]SM-108 was incubated in the enzyme solution with PRPP and MgCl2. This conversion by enzyme was also inhibited by adenine. Viewed together, these results strongly suggest that SL-1250 is, after being converted to SM-108, activated to its nucleotide form by adenine phosphoribosyltransferase (EC 2 4.2.7) and that this SM-108 nucleotide blocks de novo synthesis of guanosine 5'-monophosphate by inhibiting IMP dehydrogenase. (Author abstract) (9 Refs)

29. CHARACTERISTICS OF DOXORUBICIN TRANSPORT IN HUMAN RED BLOOD CELLS.

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Scand J Clin Lab Invest; 41(7):633-639 1981

The transport characteristics of doxorubicin (DR:adriamycin) efflux from human erythrocytes was measured by spectrophotofluorometric determination of the net efflux into DR-free medium at 37 C. Low concentrations of phloretin, 1-alcohols, local anesthetics, HgCl2, LaCl3, p-chloromercuribenzoate, and pyridoxal-5-phosphate were added to the medium to examine their effects on DR efflux. DR efflux decreased with pH and increased with increasing chain length of 1-alcohols, with cationic, anionic, and electroneutral anesthetics, but was little affected by various inhibitors of facilitated transport systems, indicating that proteins are not involved in DR transport. The data are consistent with the perception of DR transport as a Fickean diffusion transport process of the electroneutral (unprotonated) DR molecule through the lipid domain of the cell membrane. (30 Refs)

30. INTRACELLULAR PHOSPHATE AND ITS POSSIBLE ROLE AS AN EXCHANGE ANION FOR ACTIVE TRANSPORT OF METHOTREXATE IN L1210 CELLS.

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Biochem Biophys Res Commun; 104(2):474-482 1981

Intracellular phosphate (Pi) transport in the absence of added Na was examined in mouse L1210 leukemia cells in N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid buffer. 33Pi uptake was compared in samples at 37 C and 4 C. A double reciprocal plot of the data yielded a transport kinetic constant of 1.7 milli(m)M for half-maximal transport; the maximal rate of transport was 50 picomoles/min/mg protein. Inhibition of 33Pi influx by increasing amounts of unlabeled Pi confirmed that 33Pi uptake was primarily carrier mediated. Methotrexate (MTX) also inhibited Pi uptake in the absence of added Na. The Pi transport component affected by MTX represented approx 50% of the total uptake. Pi transport was partially inhibited by preincubation with carbodiimide-activated MTX, but the remaining 50% of activity was unaffected by subsequent addition of MTX. The Na-dependent transport system of L1210 cells was inhibited by various anions in the order of effectiveness Pi greater than phyrophosphate greater than arsenate greater than sulfate greater than AMP = MTX. Pi evidently enters L1210 cells by at least two transport systems: a low-capacity Na-dependent route that can be inhibited by MTX, and a high-capacity, MTX-insensitive system requiring Na that is comparable to the Pi transport systems in other mammalian cells. (20 Refs)

31. ROLE OF MEMBRANE TRANSPORT IN THE PHARMACOLOGIC ACTION OF ANTIFOLATES.

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Lab. Molecular Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cancer Treat Rep; 65(Suppl1):19-27 1981

The property of accumulating and maintaining pharmacologically effective intracellular levels of folate analogs is different among proliferative tissues, both normal and tumorous, in mice. The higher sensitivity of the small intestine compared to bone marrow for folate analogs is related to greater retention of unbound drug and more prolonged inhibition of DNA synthesis in the former. Similar differences favoring greater retention of drug and more prolonged inhibition of DNA synthesis in responsive tumors compared to nonresponsive tumors and small intestine appear to account for the selective antitumor action of these agents in murine tumor models. The observed pharmacokinetic differences among tissues are largely attributable to differences in the structural specificity of carrier-mediated membrane transport of folate analogs. (Author abstract) (25 Refs)

32. MEMBRANE TRANSPORT CONSIDERATIONS IN HIGH-DOSE METHOTREXATE REGIMENS WITH LEUCOVORIN RESCUE.

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Dept. Medicine, Medical Coll. Virginia, Richmond, VA, 23298
Cancer Treat Rep; 65(Suppl1):13-17 1981

The role of membrane transport in the control of the intracellular methotrexate (MTX) component is discussed. Free intracellular MTX levels are limited by electrostatic forces as well as an asymmetrical transport carrier system. In addition, energy is coupled either to this carrier system or to an independent exit mechanism to limit the accumulation of free intracellular drug as suggested by the observation that a variety of metabolic poisons augment rather than retard the free intracellular MTX level. Thus, a variety of passive and active factors limit the accumulation of free intracellular MTX, the drug component that is required for inhibition of tetrahydrofolate synthesis. Interactions between leucovorin (LV) and MTX at the level of the membrane transport system in rescue regimens are discussed. High-dose LV rescue offers the opportunity for delivering high levels of LV into the cell and the potential for eliminating the pharmacologic effect of MTX as well. Other topics discussed include the following: administration of MTX as a bolus vs an iv infusion, high-dose MTX and the solid tumor, and MTX polyglutamates and their potential role in drug cytotoxicity and selectivity. (35 Refs)

33. BIOCHEMICAL CRITERIA USED FOR PROGNOSIS OF EFFICACY OF CHEMOTHERAPY OF TUMORS.

Gerasimova GK, Matveev LV, Mokina VD
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (12):15-19 1981

Biochemical mechanisms of different sensitivity of tumor cells to antineoplastic agents are discussed. In vitro and in vivo experiments showed that the incorporation of the labeled analog of mercaptopurine (MP) into DNA of L1210 leukemia cells resistant to MP was significantly lower than that in the sensitive cells. Increased MP incorporation was also observed in cells of highly sensitive adenocarcinoma Ac-755. Development of resistance to fluorouracil (FU) was associated with decreased FU incorporation into RNA. The cells resistant to FU retained the sensitivity to cytarabine and carminomycin. At the same time, development of resistance to FU was associated with the significant decrease of the sensitivity to methotrexate (MT), hydroxyurea, guanazole, and 5-azacytidine. Administration of methionine synthetase inhibitor was found to increase sensitivity of Ehrlich ascites carcinoma cells to MT. These findings indicate the role of folic acid cycle and conjugated reactions of thymidilate biosynthesis in the sensitivity of tumor cells to antimetabolites. (9 Refs) (In RUS)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

34. IRON-BLEOMYCIN-DNA-SYSTEM. EVIDENCE OF A LONG-LIVED BLEOMYCIN-IRON-OXYGEN INTERMEDIATE.

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Biochem Biophys Res Commun; 104(2):557-563 1981

Addition of Fe(II) to bleomycin (BLM) in the presence of DNA at a concentration of 4 x 10(-3) M or higher yields a species (I') with a half-life of approx 50 min which is electron paramagnetic resonance silent and which consumes 1 mole of oxygen per mole of iron when formed at 25 C. The I' complex evolves over time, ultimately yielding an Fe(III).BLM complex (III'). Spectroscopic analyses show that the presence of DNA stabilizes complex III', probably by a combination of binding DNA base trans to the oxygen and building a protective pocket around the metal as in hemoproteins. (10 Refs)

35. NUCLEAR CATALYZED ANTIBIOTIC FREE RADICAL FORMATION.

Bachur NR, Gee MV, Friedman RD

Lab. Clinical Biochemistry, Baltimore Cancer Res. Program, NCI, Baltimore, MD, 21201

Cancer Res; 42(3):1078-1081 1982

Nuclei isolated from rat liver, heart, and kidney catalyze oxygen consumption in the presence of reduced pyridine nucleotide (NADPH) and quinone or quinone-imine antibiotics such as Adriamycin, daunorubicin, actinomycin D, mitomycin C, and streptonigrin. The Km and Vmax values for NADPH were 2.4 x 10(-3) M and 3 x 10(-8) mol O2 per min per mg protein and Km values for the antibiotics ranged from 1.4 x 10(-4) M to 5.9 x 10(-6) M. Metabolism of the anthracycline antibiotics, ie, reductive glycosidase reaction, occurs in reaction mixtures after all oxygen is consumed. During the reaction, free-radical species of Adriamycin and daunorubicin are detectable by electron paramagnetic resonance spectrometry. These observations indicate that some cytotoxic antibiotics can be activated to a free-radical state at the site where damage to nuclear DNA may result. (Author abstract) (23 Refs)

36. A COMPARISON OF THE LETHAL AND KINETIC EFFECTS OF DOXORUBICIN AND 4'-EPI-DOXORUBICIN IN VITRO.

Hill BT, Whelan RD

Lab. Cellular Chemotherapy, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England

Tumori; 68(1):29-37 1982

In vitro lethal and kinetic effects of 4'-epi-doxorubicin (EPI-DXR) have been established and compared with those of doxorubicin (14-hydroxy-daunorubicin, adriamycin, NSC-123127, DXR). Both drugs show comparable cytotoxicity against a range of murine and human cell lines. Cytotoxicity increased exponentially with drug concentration and with duration of exposure. EPI-DXR like DXR exerts maximal lethal effects during the late S and G2 phases of the cycle in synchronized NIL8 Syrian hamster cells. Flow microfluorimetric data and measurements of mitotic indices provide evidence of population arrest in G2 with both drugs. Responses of various drug-resistant L5178Y cell lines were similar for DXR and EPI-DXR: (i) DXR-resistant cells exhibit complete cross-resistance to EPI-DXR, (ii) vincristine-resistant cells are cross-resistant to DXR and EPI-DXR, and (iii) methotrexate-resistant and 5-fluorouracil-resistant cells show collateral sensitivity to both drugs. These studies emphasize the similarities of DXR and EPI-DXR. (Author abstract) (34 Refs)

37. RING-HYDROXYLATED ANALOGUES OF LUCANTHONE AS ANTITUMOR AGENTS.

Archer S, Miller KJ, Rej R, Periana C, Fricker L

Chemistry Dept., Cogswell Lab., Rensselaer Polytechnic Inst., Troy, NY, 12181

J Med Chem; 25(3):220-227 1982

A series of ring-alkoxylated and ring-hydroxylated analogues of lucanthone was prepared and tested for antitumor activity. The most biologically interesting members of this group were the 7-hydroxylucanthone derivatives, 50 and 51, which gave T/C values in the NCI P-388 antitumor screen of 188 and 265, respectively. The apparent association constants and deltaTm values for a number of analogue-DNA complexes were determined to ascertain whether there was any quantitative correlation with biological activity. The most that can be said is that intercalation may be a necessary but far from sufficient condition of antitumor activity. (Author abstract) (20 Refs)

38. TOXICITY, INTERSTRAND CROSS-LINKS AND DNA FRAGMENTATION INDUCED BY ACTIVATED' CYCLOPHOSPHAMIDE IN YEAST: COMPARATIVE STUDIES ON 4-HYDROXYPEROXY-CYCLOPHOSPHAMIDE, ITS MONOFUNCTIONAL ANALOGON, ACROLEIN, PHOSPHORAMIDE MUSTARD, AND NOR-NITROGEN MUSTARD.

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Chem Biol Interact; 39(1):1-15 1982

Activated cyclophosphamide (CP) is known to achieve its cytotoxic and alkylating capacity upon spontaneous hydrolytic breakdown of the oxazaphosphorine ring structure. Treatment of yeast cells with the chemically activated form of CP (4-hydroperoxy-CP, 4-OOH-CP) and with several potentially toxic cleavage products revealed that cytotoxicity is closely linked to the formation of DNA interstrand cross-links and to DNA fragmentation. While this holds true for 4-OOH-CP and its bifunctional alkylating breakdown products, phosphoramide mustard (PM) and nor-nitrogen mustard (NNM), equimolar concentrations of acrolein and the monofunctional analogon of activated CP were inactive. NNM, the ultimate cleavage product within the successive degradation of the oxazaphosphorine structure was 5x more toxic than 4-OOH-CP, whereas the cytotoxic action of PM was only slightly enhanced. The high cytotoxicity of NNM was matched by its ability to induce DNA interstrand cross-links: at concentrations and treatment times producing equal cell killing, 4-OOH-CP and NNM produced the same extent of cross-linking and DNA fragmentation. Biochemical potency of NNM is in contrast to data found with the NBP colorimetric assay which suggest that NNM loses its alkylating activity at neutral pH. 4-OOH-CP and PM are much more stable than predicted from half-life measurements performed via the NBP colorimetric assay: they retain a considerable fraction of their cytotoxic and cross-linking activity in spite of a 12-hr preincubation at pH 7 and 36 C. (Author abstract) (24 Refs)

39. INHIBITORY EFFECTS OF VARIOUS 5-HALOGENATED DERIVATIVES OF 1-BETA-D-ARABINOFURAN OSYLURACIL 5'-TRIPHOSPHATE ON DNA POLYMERASES FROM MURINE CELLS AND ONCORNAVIRUS: SUBSTITUENT EFFECTS ON INHIBITORY ACTION.

Ono K, Ogasawara M, Ohashi A, Matsukage A, Takahashi T, Nakayama C, Saneyoshi M
Lab. Viral Oncology, Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya 464, Japan
Biochemistry; 21(5):1019-1024 1982

The effects of four 5-halogenated derivatives of 1-beta-D-arabinofuranosyluracil 5'-triphosphate (aUTP) on the activity of DNA polymerases from mouse cells and oncornavirus were examined in comparison with that of the mother compound, aUTP, and also with those of the sister compounds, 5-alkylated derivatives of aUTP. The newly synthesized and tested compounds in this study were 1-beta-D-arabinofuranosyl-5-fluorouracil 5'-triphosphate (aFUTP), 1-beta-D-arabinofuranosyl-5-chlorouracil 5'-triphosphate (aClUTP), 1-beta-D-arabinofuranosyl-5-bromouracil 5'-triphosphate (aBrUTP), and 1-beta-D-arabinofuranosyl-5-iodouracil 5'-triphosphate (aIUTP). The results are summarized. Relationships between the chemical structures of the analogues and their inhibitory effects are discussed according to inductive, hydrophobic, and steric characteristics of the substituents on the 5 position of the uracil nucleus. It was concluded that both steric and hydrophobic effects of the halogen substituents were important for the inhibition of all DNA polymerases and that the inductive effect of halogen atoms was clearly observed for DNA polymerase beta with activated DNA and RLV DNA polymerase with (rA)n.(dT)12-18. (22 Refs)

EFFECTS OF ANTIMETASTATIC AGENTS

40. CANCER CELL PROCOAGULANT: A NOVEL VITAMIN K-DEPENDENT ACTIVITY.

Delaini F, Colucci M, De Bellis Vitti G, Locati D, Poggi A, Semeraro N, Donati MB
Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea, 62, 20157 Milan, Italy
Thromb Res; 24(3):263-266 1981

Further elaboration of the unexplained, vitamin K-deficiency related, reducing metastasis of 3LL tumors was reported. Four sets of C57Bl/6J mice, the original source of the 3LL tumor, were used and all given 3LL-cell leg implants at day 0: 1. control with neomycin-supplemented diet, 2. as in 1. but diet deficient in vitamin K, and initiated 7 days before day 0, 3. warfarin present in drinking water from day 7, 4. as in 3. but vitamin K3 also in the water from day 14. All animals were sacrificed on day 17 and the primary tumor cells harvested. The tumor cell procoagulant activity (innate ability of 3LL cells to directly activate coagulation factor X) and thrombotest result were both 2. = 3. much less than 1. = 4. Since it had already been suggested that activated factor X might be responsible for fibrin deposition and thus contribute to metastasis, it was now suggested that the antimetastatic role of warfarin be reevaluated. (8 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

41. RAPID FORMATION OF POLY-GAMMA-GLUTAMYL DERIVATIVES OF METHOTREXATE AND THEIR ASSOCIATION WITH DIHYDROFOLATE REDUCTASE AS ASSESSED BY HIGH PRESSURE LIQUID CHROMATOGRAPHY IN THE EHRLICH ASCITES TUMOR CELL IN VITRO.

Fry DW, Yalowich JC, Goldman ID
(c/o Goldman) Dept. Medicine, Medical Coll. Virginia, Richmond, VA, 23298
J Biol Chem; 257(4):1890-1896 1982

The intracellular synthesis and retention of polygammaglutamyl derivatives of methotrexate, 4-amino-10-methylpteroylglutamate (4-NH2-10-CH3-PteGlu1), and their interactions with dihydrofolate reductase were evaluated in the Ehrlich ascites tumor cell in vitro by high pressure liquid chromatography. The accumulation of these metabolites was increased over five-fold by the addition of 5 mM L-glutamate or L-glutamine and exhibited a positive correlation with the extracellular concentration of methotrexate. Derivatives having from 1 to 5 glutamyl residues (4-NH2-10-CH3-PteGlu2-6) were detected and accumulation occurred in a distinctive pattern. 4-NH2-10-CH3-PteGlu2 appeared rapidly and reached a steady state level within 60 min which persisted over 4 hr. The appearance of 4-NH2-10-CH3-PteGlu3 and -Glu4 was detected after short lag periods and their levels continued to increase for at least 4 hr becoming the predominant derivatives within the cell. Higher derivatives (4-NH2-10-CH3-PteGlu5 and -Glu6) were detected after 1 hr; however, their levels remained low. As the levels of intracellular methotrexate polyglutamate derivatives increased, there was a decline in intracellular methotrexate. Studies employing gel filtration show that this was due, at least in part, to the replacement of methotrexate on dihydrofolate reductase by its metabolites and the subsequent efflux of the previously bound methotrexate from the cell. The percentage of polyglutamate derivatives bound to dihydrofolate reductase was similar to the percentage of nonbound derivatives, indicating a high affinity of these metabolites for this enzyme. When polyglutamate derivatives were in excess of the dihydrofolate reductase binding capacity and extracellular methotrexate was removed, methotrexate rapidly exited the cell whereas the majority of its metabolites were retained and eventually saturated the majority of the enzyme. Although methotrexate polyglutamates were detected in the extracellular compartment, a chemical gradient (inside/outside) of over 200 was maintained across the membrane. These studies indicate that (1) intracellular methotrexate is rapidly converted to poly-gamma-glutamyl derivatives, (2) these metabolites effectively compete with methotrexate for binding on dihydrofolate reductase, and (3) these derivatives are retained within the cell more effectively than methotrexate. (Author abstract) (31 Refs)

INTERFERON AND OTHER ANTIVIRALS

42. CYTOGENETIC ANALYSIS OF MOUSE BONE MARROW RADIOPROTECTION WITH INTERFERON INDUCE R POLY-I-POLY-C.

Zhukova NA, Palyga GF, Maksimenko AA, Zavitaeva TA
Res. Inst. Medical Radiology, Obninsk, USSR
Stud Biophys; 86(3):205-210 1981

The radioprotective effect of interferon inducer poly I-C was studied in male (CBA x C57BL)F1 mice. Animals were subjected to whole-body gamma irradiation with 100, 200, and 400 rads; 48 hr prior to irradiation, animals were injected ip with poly I-C (0.2 ml). Prophylaxis administration of poly I-C reduced the incidence of chromosome aberrations in the bone marrow of irradiated mice. The most pronounced decrease of the frequency of chromosome and chromatid aberrations was observed after irradiation with 400 rads. (11 Refs) (In RUS)

43. INTERFERON-INDUCED ANTIVIRAL ACTIONS IN FRIEND LEUKEMIA CELLS: ROLE OF MEMBRANE GANGLIOSIDES.

Belardelli F, Aliberti A, Santurbano B, Antonelli G, D'Agnolo G, Rossi GB
Servizio Biologico, Istituto Superiore di Sanita, Rome, Italy
Virology; 117(2):391-400 1982

The interactions between interferon (IFN) and membrane gangliosides have been analyzed in Friend leukemia cells (FLC). The GM1-cholera toxin (CT) model has been selected as a reference system for a high-affinity ganglioside-ligand binding. Two gangliosides have been detected in FLC extracts: a disialoganglioside (approx 95%) and a monosialoganglioside (approx 5%) which migrate respectively as GD1a and GM1. Unilammellar liposomes containing either mixed commercial gangliosides or GD1a or GM1 bind three to eight fold more IFN (both partially purified and pure) than gangliosides-free liposomes. Only 3-4% of the input IFN was bound, whereas GM1-containing liposomes bound almost 50% of $[^{3}H]$acetyl-CT. Neuraminidase treatment of FLC, which converts GD1a-like into the GM1-like ganglioside, does not significantly modify the IFN-induced antiviral effects. CT binding to FLC as well as CT-induced elevation of endocellular cyclic AMP levels in FLC were instead markedly increased by the same neuraminidase treatment. Further, pretreatment of FLC with either GD1a or GM1 or gangliosides extracted from FLC did not change the IFN-induced establishment of the antiviral state. These data provide convincing evidence that FLC gangliosides do not represent the IFN high-affinity receptors nor specifically mediate IFN effects, even though they bind IFN to some extent. (Author abstract) (26 Refs)

44. MECHANISM OF INTERFERON ACTION. DIFFERENTIAL EFFECT OF INTERFERON ON THE SYNTHESIS OF SIMIAN VIRUS 40 AND REOVIRUS POLYPEPTIDES IN MONKEY KIDNEY CELLS.

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Virology; 117(2):379-390 1982

The effect of interferon (IFN) treatment on the synthesis of viral proteins was examined in BSC-1 monkey kidney cells singly and doubly infected with simian virus 40 (SV40) and reovirus . The pattern and amount of SV40 T antigen and reovirus lambda, mu, and sigma polypeptide synthesis was comparable in singly and doubly infected cells in the absence of IFN treatment. As determined by Yakobson et al and Kingman and Samuel SV40-specific RNA synthesis is inhibited by treatment of cells with IFN before infection, but is not inhibited by IFN treatment after infection. IFN treatment initiated before infection inhibited the synthesis of both SV40 T antigen and reovirus polypeptides. However, SV40 T antigen synthesis was not inhibited in SV40 wt or tsA mutant-infected cells when treated with monkey kidney or human leukocyte IFN after infection. By contrast, reovirus polypeptide synthesis was markedly inhibited in BSC-1 cells treated with IFN after SV40 infection and superinfected with reovirus. SV40 infection did not rescue reovirus polypeptide synthesis from the inhibitory action of IFN, and reovirus infection did not alter the resistance of SV40 T antigen synthesis to IFN in cells IFN-treated after SV40 infection. Total cellular protein synthesis was not significantly affected by IFN treatment. These results suggest that the interferon-induced inhibitor(s) of protein synthesis discriminate between SV40 and reovirus mRNAs; the translation of SV40 mRNA, like most cellular mRNAs, is not affected under conditions where the IFN-induced inhibitor(s) significantly affect the translation of reovirus mRNA. (Author abstract) (40 Refs)

45. LOW LEVELS OF INTERFERON IN THE CULTURE MEDIUM OF MOUSE K/BALB CELLS: DETECTION BY THE INDUCTION OF 2-5A-SYNTHETASE IN L-929 CELLS.

Hovanessian AG, Robert N
Unite d'Oncologie Virale, Institut Pasteur, 75724 Paris Cedex 15, France
Ann Virol; 132(2):189-194 1981

Capacity of the culture medium of K/Balb cells to induce pppA(2'p5'A)n synthetase (2-5A synthetase) in L-929 mouse cells which contain low levels of 2-5A synthetase without treatment with interferon (IFN), was measured. The level of 2-5A synthetase in L-929 cells after 24-hr treatment was 1286 picomole/mg/hr, a level which was routinely induced by 10-20 effective units of IFN. Culture medium from NIH/3T3 with very low 2-5A synthetase levels did not modify the level in control L-929 cells. Induction of 2-5A synthetase by culture medium indicated that K/Balb cells produce low amounts of IFN which is probably responsible for the presence of the enzyme in such cells. The inducer of 2-5A synthetase was not extractable by phenol. Heating the K/Balb medium at 75 C for 45 min resulted in the loss of the enzyme inducing activity, which is in accordance with the loss of both antiviral and 2-5A synthetase-inducing activities of IFN when heated at the same temperature. The action of the 2-5A synthetase inducer was blocked in the presence of beta-IFN, and by actinomycin D and cycloheximide when added at the start of treatment. Addition of these inhibitors 3 hr after the start of treatment resulted in the inhibition only in the case of cycloheximide. Results indicated that both transcriptional and translational processes were required for the induction of 2-5A synthetase in mouse L-929 cells by culture medium of K/Balb cells, and that the inducer was species specific. This assay may provide a useful, reproducible, and sensitive assay for the detection of trace amounts of IFN. (14 Refs)

46. PROTEIN KINASE (PP67-INF) IN PLASMA AND TISSUE OF MICE WITH HIGH LEVELS OF CIRCULATING INTERFERON.

Hovanessian AG, Riviere Y, Robert N, Svab J, Chamaret S, Guillon JC, Montagnier L
Departement de Virologie, Institut Pasteur, 75724 Paris Cedex 15, France
Ann Virol; 132(2):175-188 1981

Mouse L-929 cells were treated with interferon (IFN) and the enhanced protein kinase activity manifested by the phosphorylation of the endogenous 67,000 mol wt phosphoprotein (pp67-IFN) was studied. Levels of circulating IFN, of pppA(2'p5'A)n synthetase (2-5A synthetase), of pp67-IFN kinase in the spleen and plasma of mice inoculated with Newcastle disease virus, of encephalomyocarditis virus, of poly(I)poly(C), or of poly(A)poly(U), were measured. Levels of these enzymes were enhanced in accordance with the level of circulating IFN, reaching the max 15-18 hr after IFN reached the peak for 2-5A synthetase, and 24 hr for pp67-IFN kinase. 2-5A synthetase could not b detected in the mice serum or plasma prepared with sodium citrate, even when they showed high levels of 2-5A synthetase and pp67-IFN kinase in their liver and spleen. Amino acids involved in the phosphorylation of pp67-IFN from three different sources were investigated. The pp67-IFN were phosphorylated mostly by their serine residues. Threonine residues were also phosphorylated but at much lower levels, and no phosphorylation of tyrosine residues was observed. The phosphorylations were carried out in vitro. Results indicate the significance of the pp67-IFN kinase measurement for testing the response of an organism to IFN or IFN-inducers, and the possible existence of a saturation point for the IFN action beyond which the tested system does not respond. (17 Refs)

47. INTERFERON INHIBITS SENDAI VIRUS-INDUCED CELL FUSION: AN EFFECT ON CELL MEMBRANE FLUIDITY.

Chatterjee S, Cheung HC, Hunter E
Dept. Microbiology, Univ. Alabama, University Station, Birmingham, AL, 35294
Proc Natl Acad Sci USA; 79(3):835-839 1982

Interferon can affect several cellular functions, in addition to its antiviral activity. We report here that pretreatment of human cells with homologous interferon significantly inhibits cell fusion induced by Sendai virus and that this refractory state is accompanied by a decrease in cell plasma membrane fluidity. Multinucleate cell formation induced by beta-propiolactone-inactivated Sendai virus in human fibroblast cells (a system in which fusion results from an interaction of the viral glycoprotein with the cell membrane) was inhibited by more than 90% after addition of human interferon for 18-24 hr. This inhibition could be neutralized by antiserum to interferon. Furthermore, inhibitor studies with cycloheximide and actinomycin D clearly indicated that synthesis of protein and RNA is necessary to establish the resistant state. To determine whether the inhibition of Sendai virus-induced cell fusion resulted from interferon-induced changes at the cell plasma membrane, experiments were carried out using the fluorescence probe 1,6-diphenyl-1,3,5-hexatriene, which is capable of sensing molecular motions in the hydrocarbon core of the bilayer structure. A significant decrease in the membrane fluidity of interferon-treated cells was observed. It is likely, therefore, that the inhibitory effect on Sendai virus-induced cell fusion observed in interferon-treated cells results from an increased rigidity of the target cell membrane. (Author abstract) (31 Refs)

48. VIRUS-MEDIATED INHIBITION OF THE PPP(A2'P)NA SYSTEM AND ITS PREVENTION BY INTERFERON.

Cayley PJ, Knight M, Kerr IM
Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London WC2A 3PX, England
Biochem Biophys Res Commun; 104(2):376-382 1981

A radioactive analog ppp(A2'p)3A(32P)pCp of the oligonucleotide ppp(A2'p)nA (where n = 2 to 4 or more; known collectively as 2-5A) was synthesized and bound to the 2-5A binding protein in Ehrlich ascites tumor, human HeLa cells, and mouse L-cells with encephalomyocarditis virus. Radiobinding assay showed that 2-5A-dependent nuclease activity in these cells is usually lost after EMC infection, relatively early in the growth cycle. Prior treatment with interferon can partially or completely prevent the loss. It may be the prevention of virus-mediated inhibition of 2-5A-dependent nuclease, rather than the induction of 2-5A synthetase, that is crucial for interferon effectiveness in activating the 2-5A system. (18 Refs)

49. INDUCER-RESPONSIVE EXPRESSION OF THE CLONED HUMAN INTERFERON BETA1 GENE INTRODUCED INTO CULTURED MOUSE CELLS.

Ohno S, Taniguchi T
Dept. Biochemistry, Cancer Inst., Japanese Foundation Cancer Res., Tokyo 170, Japan
Nucleic Acids Res; 10(3):967-977 1982

A hybrid plasmid was constructed from pSV2-Egogpt and the cloned 1.8 kilobase chromosomal DNA segment which contains the human interferon (HIFN-beta1) gene and its flanking sequences. Cultured mouse FM3A cells were transfected by the hybrid plasmid and several Ecogpt clones were selected. Southern blot analysis of the DNA from these mouse cell clones showed that two of them contained a few copies of the 1.8 kilobase human DNA. Synthesis of mRNA characteristic of the HIFN-beta1 mRNA increased as measured by RNA blot analysis when those clones were treated with Newcastle disease virus or with poly(I):poly(C). In addition, the induced mouse cell clones gave rise to the synthesis of human IFN-beta1. These results suggest the presence of a unique nucleotide sequence in the 1.8 kilobase DNA which is sufficient for the inducer-responsive expression of the human IFN-beta1 gene. (Author abstract) (30 Refs)

50. 2'-5' OLIGO(A) SYNTHETASE LEVELS IN INTERFERON-SENSITIVE OR -RESISTANT LYMPHOID CELLS.

Kollais SI, Kortsaris A
Dept. Cell Biology and Virology, Theagenion Medical Inst., Thessaloniki, Greece
J Gen Virol; 58(part1):191-193 1982

The activity of 2'-5' oligo(A) synthetase has been measured both in control and interferon-treated lymphoid cells. While control or interferon-treated Raji and Namalwa cells exhibit low activity of the 2'-5' oligo(A) synthetase, the activity of this enzyme is increased 20-fold when Daudi cells are treated with the same dose of human interferon. The same enzyme is induced by interferon in R3HR-1 cells to a lesser extent. (Author abstract) (19 Refs)

51. PREVENTION OF INTERFERON-INDUCED AUGMENTATION OF CELLULAR ANTITUMOR EFFECTOR MECHANISMS BY PHORBOL ESTERS.

Keller R, Aguet M, Tovey M, Stitz L
Immunobiology Res. Group, Inst. Immunology and Virology, Univ. Zurich, Schonleinstrasse 22, CH-8032 Zurich, Switzerland
Cancer Res; 42(4):1468-1472 1982

Both natural killer cell- and macrophage-mediated spontaneous in vitro cytotoxicity for tumor targets is rapidly and strongly augmented by interferon. Macrophage-activating lymphokines considerably enhance macrophage-tumoricidal activity but did not affect natural killer cell-type cytotoxicity. Augmentation of cytolytic capacity by interferon and by macrophage-activating lymphokines is prevented by the tumor-promoting phorbol ester, 12-O-tetradecanoylphorbol-13-acetate. However, the classical antiviral activity and the specific binding of interferon to cell surface receptors remains unaffected by 12-O-tetradecanoylphorbol-13-acetate. (Author abstract) (27 Refs)

52. MUTATIONS IN THE HERPES SIMPLEX VIRUS DNA POLYMERASE GENE CAN CONFER RESISTANCE TO 9-BETA-D-ARABINOFURANOSYLADENINE.

Coen DM, Furman PA, Gelep PT, Schaffer PA
Dept. Microbiology and Molecular Genetics, Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115
J Virol; 41(3):909-918 1982

Mutants of herpes simplex virus type 1 resistant to the antiviral drug 9-beta-D-arabinofuranosyladenine (araA) have been isolated and characterized. Ara-A-resistant mutants can be isolated readily and appear at an appreciable frequency in low-passage stocks of wild-type virus. Of 13 newly isolated mutants, at least 11 were also resistant to phosphonoacetic acid (PAA). Of four previously described PAA-resistant mutants, two exhibited substantial araA resistance. The araA resistance phenotype of one of these mutants, PAAr5, has been mapped to the HpaI-B fragment of herpes simplex virus DNA by marker transfer, and araA resistance behaved in marker transfer experiments as if it were closely linked to PAA resistance, a recognized marker for the viral DNA polymerase locus. PAAr5 induced viral DNA polymerase activity which was much less susceptible to inhibition by the triphosphate derivative of araA than was wild-type DNA polymerase. These genetic and biochemical data indicate that the herpes simplex virus DNA polymerase gene is a locus which, when mutated, can confer resistance to araA and thus that the herpes simplex virus DNA polymerase is a target for this antiviral drug. (Author abstract) (41 Refs)

53. PYROPHOSPHATE ANALOGUES AS INHIBITORS OF DNA POLYMERASES OF CYTOMEGALOVIRUS, HERPES SIMPLEX VIRUS AND CELLULAR ORIGIN.

Eriksson B, Oberg B, Wahren B
Dept. Antiviral Chemotherapy, Res. and Development Lab., Astra Lakemedel AB, Sodertalje, Sweden
Biochim Biophys Acta; 696(2):115-123 1982

Several pyrophosphate analogues have been compared for their ability to inhibit the activities of isolated cytomegalovirus (CMV) DNA polymerase, herpes simplex virus Type 1 (HSV 1) DNA polymerase and calf thymus DNA polymerase alpha. The most effective inhibitors were phosphonoformate and phosphonoacetate. Although not identical, the structural requirements for compounds inhibitory to CMV and HSV-1 DNA polymerase were specific, with two negatively charged groups in close vicinity. The CMV DNA polymerase was more susceptible to certain phosphonoacetates containing bulky hydrophobic alpha-substituents than was the HSV-1 DNA polymerase. No example of the converse preference was found. The inhibition of CMV DNA polymerase by phosphonoformate, hypophosphate, alpha-hydroxyphosphonoacetate and alpha-nonylphosphonoacetate was linear non-competitive with the deoxyribonucleoside triphosphates as variable substrates. Phosphonoformate, phosphonoacetate, and to a lesser extent alpha-hydroxyphosphonoacetate, carbonyldiphosphonate and alpha-nonylphosphonoacetate also inhibited the focus formation by CMV in cell-culture. (Author abstract) (33 Refs)

OTHER RELATED STUDIES

54. BIOLOGICAL RESPONSE MODIFIERS IN CANCER THERAPEUTICS.

Mihich E
Grace Cancer Drug Center, New York State Dept. Health, Roswell Park Memorial Inst., Buffalo, NY
Cancer- Achievements, Challenges, and Prospects for the 1980s, Proceedings of an International Conference held in New York, 14-16 September, 1980. Vol. 2, Memorial Sloan-Kettering Cancer Center New York, NY. Burchenal, J. H. and Oettgen, H. F., eds. (New York, Grune and Stratton), 944 pp., 1981.

Immunostimulating and immunomodulating agents, both natural and synthetic, thymic factors, and interferons as biological response modifiers (BRMs) in cancer therapeutics are reviewed. Suggestions are made for research on the mode of action and prerequisites for BRM action, with special reference to Phase I and II studies. (17 Refs)

55. ANTIMETABOLITES.

Schilsky RL, Jolivet J, Chabner BA
Harry Truman Veterans Admin. Hosp., Columbus, MO, 65201
Cancer Chemotherapy 1981- The EORTC Cancer Chemotherapy Annual 3. Pinedo HM, ed. Amsterdam, Excerpta Medica, 504 pp, 1981.

Mechanisms of action and pharmacokinetics were stressed in discussing methotrexate (and some new antifolates), fluoropyrimidines (FLP), cytosine arabinoside (and new analogs), 5-azacytidine, pyrazofurin, hydroxyurea, and purine analogs. FLP included 5-deoxy-5-fluorouridine, ftorafur, thymidine (TdR), and the drug interactions with TdR, allopurinol, and testosterone. The mechanism of action of 5-fluorouracil is treated in detail. (122 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/122

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Mechanisms of Action

SERIES CB19 No. 82/08

AUGUST, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HE 20. 3173/2:

EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. MECHANISM OF TOXICITY OF PLATINUM (II) COMPOUNDS IN REPAIR-DEFICIENT STRAINS OF ESCHERICHIA COLI.

Alazard R, Germanier M, Johnson NP

Laboratoire de Pharmacologie et de Toxicologie Fundamentales, 250, Route de Narbonne, 31078 Toulouse Cedex, France

Mutat Res; 93(2):327-337 1982

Three platinum compounds, cis-platinum diamino dichloride (cis-PDD), trans-platinum diamino dichloride (trans-PDD), and [Pt(dien)Cl] Cl (dien = H2N-CH2-CH2-NH-CH2-CH2-NH2), were studied in terms of survival experiments with 10 strains of Escherichia coli, platinum binding to DNA immediately after treatment, inhibition of DNA synthesis, and repair synthesis and toxicity of these compounds in wild-type and repair-deficient E coli strains. The three Pt compounds bind to E coli DNA in vivo. The cis- and trans-PDD exert their toxic effect by inhibition of DNA synthesis. Wild-type bacteria is able to survive by partially repairing these DNA lesions, but mutant strains cannot accomplish this repair. The lower toxicities of trans-PDD and [Pt(dien)Cl] Cl are not due to a low level of DNA binding or to a greater repair of the damaged DNA, suggesting that E coli replication is unimpaired by some Pt(II)-chloramine-DNA adducts. The relative toxicities of the three types of DNA damage appear to depend on the structure of Pt-DNA adducts as well as on the number of lesions. (21 Refs)

2. ARREST OF CHAIN GROWTH OF REPLICON-SIZED INTERMEDIATES BY APHIDICOLIN DURING RAT FIBROBLAST CELL CHROMOSOME REPLICATION.

Yagura T, Kozu T, Seno T

Dept. Immunology and Virology, Saitama Cancer Center Res. Inst., 818 Komuro, Ina-machi, Saitama 362, Japan

Eur J Biochem; 123(1):15-21 1982

The effect of aphidicolin, a specific inhibitor of DNA polymerase alpha, on size maturation of nascent DNA intermediates was studied in cultured rat fibroblast cells. Results provided the first evidence of DNA synthesis associated with merging of intermediates of larger than replicon size. Aphidicolin at a concentration (1.4 ug/ml) causing 90-95% inhibition of [3H]thymidine incorporation, resulted in accumulation of intermediates of nearly the same size as the replicon (2-5 x 10(7) Da); although the synthesis of short nascent fragments (referred to as Okazaki fragments) continued in the presence of aphidicolin, the rate of their elongation to the replicon size was greatly decreased. On removal of aphidicolin, these accumulated intermediates merged into high-mol wt DNA. This merging of the intermediates was associated with DNA synthesis in gaps between adjacent intermediates, as revealed by photolysis of bromodeoxyuridine-DNA leader with long-wave ultraviolet light; when the cells had been pulse-labeled for 5 min with bromodeoxyuridine immediately after removal of the drug, the large DNA arising from aphidicolin-arrested intermediates was cut into fragments of the original size by long-wave ultraviolet light irradiation. The arrest of chain elongation at the replicon-size by aphidicolin might be due to inhibition of this DNA synthesis in gaps, because aphidicolin did not cause degradation of nascent DNAs. (Author abstract) (37 Refs)

3. PROBABLE INVOLVEMENT OF A GLYCOCONJUGATE IN IMR-32 DNA SYNTHESIS: DECREASE OF DNA POLYMERASE ALPHA2 ACTIVITY AFTER TUNICAMYCIN TREATMENT.

Bhattacharya P, Basu S

(c/o Basu) Dept. Chemistry, Biochemistry, Biophysics Program, Univ. Notre Dame, Notre Dame, IN, 46556

Proc Natl Acad Sci USA; 79(5):1488-1491 1982

Multiple forms of DNA polymerase alpha activity (alpha1, alpha2, and alpha3) from human neuroblastoma IMR-32 cells untreated or treated with tunicamycin (3 ug/ml) were separated by DEAE-cellulose column chromatography. Loss of 40-60% of DNA polymerase alpha2 activity was observed in tunicamycin-treated cells. Ricin 1B, a subunit of intact ricin (Mr, 64,000), was found to be a specific inhibitor of DNA polymerase alpha2 isolated from control IMR-32 cells. However, DNA polymerase alpha2 isolated from tunicamycin-treated cells was insensitive to ricin 1B. Heat treatment studies at 50 C showed two completely different inactivation profiles for the DNA polymerase alpha2 enzymes isolated from the tunicamycin-treated and untreated cells. A probable involvement of a beta-linked galactose-containing carbohydrate chain in the catalytic subunit of DNA polymerase alpha2 is suggested. (Author abstract) (28 Refs)

4. MOLECULAR DOSIMETRY OF DNA DAMAGE CAUSED BY ALKYLATION. I. SINGLE-STRAND BREAKS INDUCED BY ETHYLATING AGENTS IN CULTURED MAMMALIAN CELLS IN RELATION TO SURVIVAL.

Abbondandolo A, Dogliotti E, Lohman PH, Berends F

(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands

Mutat Res; 92(1/2):361-377 1982

In cultured Chinese hamster cells, N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), N-ethyl-N-nitrosourea (ENU), ethyl methanesulfonate (EMS), and diethylsulfonate (DES) differed markedly in their induction of DNA single-strand breaks (SSB) and alkali-labile sites (ALS) when the doses were compared on a molar basis (ENNG was about 1,000x more active than the other ethylating agents), but the agents were about equally effective in inducing SSB and ALS when doses of equal cytotoxicity were used. Prolonged alkali exposure greatly increased the number of SSB. DNA from untreated cells formed SSB slowly for about 10 hr; the rate then increased, remaining constant for up to 40 hr. Cells exposed to the ethylating agents showed an accelerated, dose-dependent linear generation of SSB for 10 hr, followed by a short plateau, followed by renewed SSB formation at a constant rate which was somewhat higher than the rate observed in untreated cells. The initial phase of SSB formation was attributed to phosphotriester hydrolysis; the causes of the later phase were unidentified. Zero intercepts seemed to be a measurement of the intracellular formation of apurinic sites. The kinetics of SSB induction as a function of lysis time (1 or 21 hr) were compared for ENNG and DES. A 24-hr repair period before lysis reduced the intercept phenomenon in cells exposed to ENNG but not DES. Since DES degraded rapidly during the 1-hr exposure period, most of the 'apurinic-site' damage was induced in the initial phases of exposure and may have been repaired at its end. The types of damage observed (reparable and nonreparable apurinic sites and phosphotriesters) seemed to be of little consequence for cell survival. (26 Refs)

5. INTERACTION OF ACTINOMYCIN D, ETHIDIUM, QUINACRINE DAUNORUBICIN, AND TETRALYSINE WITH DNA: 31P NMR CHEMICAL SHIFT AND RELAXATION INVESTIGATION.

Wilson WD, Jones RL

Dept. Chemistry, Lab. Microbial Biochemical Sciences, Georgia State Univ., Atlanta, GA, 30303

Nucleic Acids Res; 10(4):1399-1410 1982

The binding of actinomycin D, ethidium, quinacrine, daunorubicin, and tetralysine to DNA has been investigated using 31P NMR. Titration of DNA with actinomycin yields a new downfield peak or overlapping peaks as would be expected from the slow dissociation kinetics of this compound. The other intercalators shift the DNA 31P signal downfield as a single exchange averaged peak. Tetralysine causes a slight upfield shift. The chemical shift titration curves for the intercalators are sigmoid curves suggesting that cooperative processes or competing effects on the chemical shift are being observed. The magnitude of the chemical shift change at saturation of DNA with the compounds is found to vary significantly and to be linearly related to the DNA base pair unwinding angle for the compounds. Analysis of 31P spin lattice relaxation times (T1) and linewidths as a function of temperature (below Tm) and titration with the above compounds indicates that T1 does not change significantly while linewidth increases with decreasing temperature and increasing bound intercalator. One interpretation of these results is that in both cases the overall motion of DNA becomes slower while the internal motion is not greatly affected. (Author abstract) (34 Refs)

6. COMPARATIVE EFFECTS OF THE 5'-TRIPHOSPHATES OF 9-BETA-(2'-AZIDO-2'-DEOXY-D-ARABINOFURANOSYL)ADENINE AND 9-BETA-D-ARABINOFURANOSYLADENINE ON DNA POLYMERASES FROM L1210 LEUKEMIA CELLS.

Allaudeen HS, Kozarich JW, Sartorelli AC

Dept. Pharmacology and Developmental Therapeutics Program, Comprehensive Cancer Center, Yale Univ. Sch. Medicine, New Haven, CT, 06510

Nucleic Acids Res; 10(4):1379-1387 1982

The compound 9-beta-(2'-Azido-2'-deoxy-D-arabinofuranosyl)adenine (arazide) causes greater and significantly more persistent inhibition of [3H]thymidine incorporation into the DNA of neoplastic cells than the related agent 9-beta-D-arabinofuranosyladenine (araA). To elucidate the mechanism(s) responsible, we compared the effects of arazide and araA 5'-triphosphates on DNA polymerases alpha and beta of L1210 leukemia cells. Both nucleoside triphosphate analogs inhibited DNA polymerase alpha activity by competing with dATP; only araATP was inhibitory to DNA polymerase beta. Arazide triphosphate was at least four times more active than araATP as an inhibitor of DNA polymerase alpha. Preincubation of DNA polymerase alpha with either agent did not result in enzyme inactivation. The results suggest that interference with DNA polymerase alpha activity by arazide triphosphate may be in part responsible for the inhibition of DNA synthesis produced by arazide in neoplastic cells. (Author abstract) (22 Refs)

7. INHIBITORS OF REPAIR DNA SYNTHESIS.

Collins AR, Squires S, Johnson RT

Cancer Res. Campaign Mammalian Cell DNA Repair Group, Dept. Zoology, Univ. Cambridge, Downing St., Cambridge, CB2 3EJ, England

Nucleic Acids Res; 10(4):1203-1213 1982

We have measured repair DNA synthesis in UV-irradiated normal human fibroblasts, grown to a defined state of quiescence in order to avoid the problem of discriminating repair from replication DNA synthesis. We have assessed the effects of various DNA synthesis inhibitors on repair. Inhibition of repair synthesis by hydroxyurea, 1-beta-D-arabinofuranosylcytosine and aphidicolin is associated with the ability to accumulate DNA breaks due to enzymic incision at DNA damage sites; the inhibition by novobiocin is in accord with its known ability to block incision. (Author abstract) (28 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

8. ANTITUMOR EFFECT OF DICYCLOHEXYLAMMONIUM SULFATE, A POTENT INHIBITOR OF SPERMIDINE SYNTHASE AGAINST P388 LEUKEMIA.

Ito H, Hibasami H, Shimura K, Nagai J, Hidaka H

Dept. Pharmacology, Mie Univ. Sch. Medicine, Tsu, Mie 514, Japan

Cancer Lett; 15(3):229-235 1982

The effect of dicyclohexylammonium sulfate (DCHA) on P388 mouse leukemia was investigated; correlation between the antitumor effect and the spermidine concentration in ascites tumor cells and spleen is discussed. Female mice of BDF1 hybrid strain were used. DCHA administered daily for 6 days starting 24 hr after tumor inoculation prolonged the survival time of mice bearing the tumor. The percentage of mean survival days of treated relative to control mice were 110.3, 133.3, 187.2, 138.5, and 118.0 at DCHA dosages of 10, 25, 50, 75, and 100 mg/kg, respectively. A dose of 50 mg/kg/day was the most effective. DCHA was non-toxic at the dose of 100 mg/kg administered daily for 6 days. The treatment of non-leukemic mice with DCHA, 50 mg/kg ip daily for 6 days, had no significant effect on av spleen wt, compared with 0.15 M NaCl treatment. Spleen wt increased by approx 30% at 7 days after the tumor inoculation. DCHA treatment did not prevent the tumor-induced increase in splenic wt. A dose of 50 mg/kg DCHA ip administered daily for 6 days caused a diminution of the increase in concentration of spermidine, with little effect on the spermidine concentration in the ascites tumor cells and spleens of mice bearing the tumor. The depletion of spermidine in the ascites tumor cells might be a cause of the suppression of tumor growth. (26 Refs)

9. MULTIPLE FORMS AND INHIBITORS OF URIDINE-CYTIDINE KINASE IN NEOPLASTIC CELLS.

Ahmed NK

Div. Biochemical and Clinical Pharmacology, St. Jude Children's Res. Hosp., Memphis, TN

Int J Biochem; 14(4):259-262 1982

Two isozymes of uridine-cytidine kinase, a rate-limiting enzyme in the salvage pathway for pyrimidine nucleotide biosysnthesis, were demonstrated in both mouse L1210 ascites leukemia and human malignant lymphoma cells by isoelectric focusing and Sepharose 6B column chromatography. Eleven compounds were tested in vitro for their ability to inhibit the uridine-cytidine kinase-catalyzed phosphorylation of uridine by ATP in kinase preparations from L1210 and human 6410 leukemia cells. The compounds tested were: 5-iodouridine, 5'-iodo-5'deoxyuridine, 5-bromouridine, 5-chlorouridine, 5-cyanouridine, 6-aminocytidine, 4-thiouridine, 5'-azido-5'-deoxycytidine, 5'-azido-5'-deoxyuridine, 5'-O-nitrouridine, and 5'-O-nitrofluorouridine. The last four compounds were effective inhibitors of the enzyme from both cell types. While various compounds are known to inhibit the de novo pathway for uridine monophosphate (UMP), none have been available as inhibitors of the salvage pathway or of uridine-cytidine kinase specifically. The 5'-azido and 5'-O-nitro analogs may have chemotherapeutic potential either administered singly or in combination with inhibitors of the de novo pathway to UMP. (14 Refs)

10. REACTIONS OF ADRIAMYCIN WITH HAEMOGLOBIN. SUPEROXIDE DISMUTASE INDIRECTLY INHIBITS REACTIONS OF THE ADRIAMYCIN SEMIQUINONE.

Bates DA, Winterbourn CC
Dept. Clinical Biochemistry, Christchurch Hosp., Christchurch, New Zealand
Biochem J; 203(1):155-160 1982

The Adriamycin semiquinone produced by the reaction of xanthine oxidase and xanthine with Adriamycin has been shown to reduce both methemoglobin and cytochrome c. In air, but not N2, both reactions were inhibited by superoxide dismutase. With cytochrome c, superoxide formed by the rapid reaction of the semiquinone with O2, was responsible for the reduction. However, even in air, methemoglobin was reduced directly by the Adriamycin semiquinone. Superoxide dismutase inhibited this reaction by removing superoxide and hence the semiquinone by displacing the equilibrium to the right. This ability to inhibit indirectly reactions of the semiquinone could have wider implications for the protection given by superoxide dismutase against the cytotoxicity of Adriamycin. Oxidation of hemoglobin by Adriamycin has been shown to be initiated by a reversible reaction between the drug and oxyhemoglobin, producing methemoglobin and the Adriamycin semiquinone. Reaction of the semiquinone with O2 gives superoxide and H2O2, which can also react with hemoglobin. Catalase, by preventing this reaction of H2O2, inhibits oxidation of oxyhemoglobin. Superoxide dismutase, however, accelerates oxidation, by inhibiting the reaction of the semiquinone with methemoglobin by the mechanism described above. Although superoxide dismutase has a detrimental effect on hemoglobin oxidation, it may protect the red cell against more damaging reactions of the Adriamycin semiquinone. (Author abstract) (27 Refs)

11. ADRIAMYCIN-INDUCED DECREASE OF MYOCARDIAL CONTRACTION RESERVE IN RATS TESTED WITH DOBUTAMINE.

Hofling B, Zahringer J, Bolte HD
Dept. Medicine, Klinikum Grosshadern, Univ. Munich, Marchioninistr. 15, 8 Munchen 70, W. Germany
Eur J Cancer Clin Oncol; 18(1):75-80 1982

Muscle-mechanical and hemodynamic properties were measured in adriamycin-treated rats and in untreated controls. The respective parameters in both animal groups could not be distinguished at rest. Using a pharmacological stress test with dobutamine a differentiation of both groups was possible: the concentration-response curve of papillary muscles from ADM-rats was lower and shifted towards higher concentrations when compared with the respective curve of untreated animals. The max hemodynamic response following an iv bolus injection of dobutamine was considerably decreased in ADM-rats as compared to untreated rats. It is concluded that the estimation of impaired myocardial function due to adriamycin might be more accurate when the contraction reserve is evaluated. (Author abstract) (32 Refs)

12. EFFECT OF CHLORAMBUCIL AND INDOMETHACIN ON GROWTH AND PROSTAGLANDIN LEVELS IN SENSITIVE AND RESISTANT WALKER CARCINOMA.

Tisdale MJ, Gibbs J, Dobrzanski RJ
Dept. Pharmacy, Univ. Aston Birmingham, Gosta Green, Birmingham B4 7ET, England
Chem Biol Interact; 39(2):221-230 1982

An analysis of the effect of combinations of chlorambucil and indomethacin or chlorambucil and prostaglandin E2 (PGE2) on the growth of alkylating agent sensitive and resistant Walker carcinoma in vitro has been made by the isobologram approach. Indomethacin alone acts as a growth inhibitor of the Walker carcinoma. High concentrations of indomethacin (5 ug/ml) act to inhibit the growth of the resistant line sub-additively with chlorambucil, whereas low concentrations act additively. For the sensitive line indomethacin acts either additively or supra-additively with chlorambucil at all concentrations employed. Both indomethacin and low concentrations of chlorambucil alone inhibit PGE2 secretion into the culture medium of both cell lines and an enhanced inhibition is seen with the combination. PGE2 itself acts as a growth inhibitor of both cell lines, although it causes greater growth inhibition of chlorambucil resistant Walker carcinoma (LD50 1.8 ug/ml) than of the sensitive line. This correlates with a greater PGE2 secretion capacity by the resistant cell line (40 pg PGE2/ml medium/10(5) cells for the resistant tumor and 17 pg PGE2/ml medium/10(5) cells for the sensitive tumor). Combinations of PGE2 with chlorambucil inhibit growth either additively or sub-additively. It seems unlikely that inhibition of PGE2 secretion is responsible for the interactive effects of chlorambucil and indomethacin, since growth inhibition produced by the combination is not reversed by PGE2 at any of the concentrations employed. Possible mechanisms of the interactive effects are discussed. (Author abstract) (18 Refs)

13. CURRENT INFORMATION ON THE MECHANISM OF ACTION OF SYNTHETIC ESTROGENS.

Rochefort H
Unite d'Endocrinologie Cellulaire et Moleculaire, I.N.S.E.R.M. (U 148), 60 rue de Navacelles et UER de Medecine, 34100 Montpellier, France
Biochimie; 64(2):89-98 1982

Synthetic antiestrogens such as tamoxifen (Nolvadex) are currently used to treat postmenopausal breast cancer. Their mechanism of action is reviewed at the cellular and molecular level, through data of the literature and the current view of the author. Synthetic antiestrogens are mostly acting directly on breast cancer cells by interacting with the estrogen receptor (RE). They prevent estrogen action by competing with estrogens on the cytosol RE. The resulting complex is partially activated resulting in its nuclear localization and a partial and dissociated stimulation of the expression of estrogen responsive genes. The explanation of the antitumoral effect of these drugs is more controversial, since the regulation of cell proliferation is not only due to estrogens but also to other hormones and factors. The antiestrogens can therefore block cancer cell growth by inhibiting estrogen action, or by a RE mediated cytotoxic effect and/or by any other mechanism involving indirect effects, or binding to other proteins than the RE. (Author abstract) (45 Refs) (In FRE)

14. NAFAZATROM (BAY G 6575) INHIBITION OF TUMOR CELL LIPOXYGENASE ACTIVITY AND CELLULAR PROLIFERATION.

Honn KV, Dunn JR
Dept. Radiation Oncology, Wayne State Univ., 210 Science Hall, Detroit, MI, 48202
FEBS Lett; 139(1):65-68 1982

The effects of nafazatrom (Bay g 6575; 1-[(2-betanaphtyloxy)ethyl]-3-methyl-2-pyrazolin-5 one) on proliferation of B16 amelanotic melanoma cells in culture were examined over a period of 14 days. Media was changed and drug was added every other day. A dose-dependent decrease in cell proliferation was observed with a minimal effective dose of 0.1 ug/ml. This effect of nafazatrom was not due to cytotoxicity. Nafazatrom also decreased [3H]thymidine incorporation into DNA. Effects of nafazatrom were examined in vivo and on tumor cell arachidonic acid metabolism. The drug inhibited lipoxygenase activity but not prostaglandin endoperoxide synthetase (cyclooxygenase + hydroperoxidase). (16 Refs)

15. EFFECT OF 6-AZAURIDINE AND PYRAZOFURIN ON FIBRINOLYSIS BY L1210 LEUKEMIC CELLS.

Novak JF
Orthopedic Res. Lab., Allegheny-Singer Res. Corp., 320 E. North Ave., Pittsburgh, PA, 15212
Oncology; 39(2):118-125 1982

The expression of plasminogen activator activity (PA) by L1210 leukemic ascitic cells, obtained from the peritoneum of BDF1 mice, increases in the terminal stages of the disease. Treatment of mice carrying advance leukemia (Day 6 following inoculation with 10(6) cells ip) with 6-azauridine (AzUR) results in prolonged survival (2-3 days) and also in increased expression of PA activity by the ascitic cell population. Similar treatment with pyrazofurin (PF), another inhibitor of orotidylate decarboxylase and of de novo pyrimidine synthesis, fails to produce either of these effects. Neither AzUR or PF, given at the early stage of tumor growth (Day 3), extend the life span nor do they cause increase of the PA activity. Thus, the elevation in PA activity following treatment with AzUR is associated with the asymptotic stage of the disease and this phenomenon correlates positively with the life-prolonging effects of this drug. An analysis of the PA activity elicited by intact cells, secretions, and cellular digests suggests that most of the activity originates on the surface of the cells. The results indicate that the described in vivo effect of AzUR, but not that of PF, on late-stage leukemia, is mediated by the changes in the fibrinolytic potential of the tumor or host cells rather than through the inhibition of the de novo pyrimidine synthesis. (Author abstract) (43 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

16. STUDIES ON LIPOSOME-ENCAPSULATED CARBOQUONE. II. EFFECT OF LIPOSOMAL ENCAPSULATION OF CARBOQUONE ON DISTRIBUTION AND CLEARANCE IN ANIMALS.

Hisaoka M, Tsukada K, Morioka T
Product Development Lab., Sankyo Co. Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140, Japan
J Pharmacobio Dyn; 5(1):18-26 1982

Carboquone (CQ) encapsulated in liposome was followed in rats and rabbits after iv injection. Plasma concentration was 3x that of free CQ, but its clearance was approx the same. Tissue distribution studies showed that the CQ-liposome concentration was increased in lung and organs with reticuloendothelial components such as liver and spleen and decreased in peripheral tissues, which may account for the high plasma content. (24 Refs)

17. EFFECTS OF PARTIALLY THIOLATED POLYCYTIDYLIC ACID AND LIPOSOMES ON IN VITRO COLONY-FORMING CELLS OF LEUKEMIC MICE.

Ho YK, Mayhew E, Preisler HD, Bardos TJ
Dept. Biophysical Sciences, State Univ. New York at Buffalo, Buffalo, NY, 14214
Cancer Res; 42(5):1740-1743 1982

Partially thiolated polycytidylic acid (MPC), an antileukemic agent, when administered to leukemic RF/UN mice inhibited the clonogenicity of bone marrow progenitor cells in a time- and dose-dependent manner. The effect of a single dose of MPC disappeared within 40 hr due to the rapid degradation of this compound in mice. When MPC was encapsulated in liposomes before injection, its activity at 19 hr after inoculation was similar to that of free MPC. The inhibitory effect of this liposome-MPC complex, however, persisted for at least 40 hr, indicating that the MPC was protected from hydrolysis by the nucleases present in blood. Drug-free liposomes increased the number of clonogenic progenitor cells, whereas a mixture of plain liposomes and MPC decreased the number of clonogenic cells to a greater extent than did MPC alone or MPC within liposomes. A possible explantation for these observations is that the liposomes per se altered the clearance function of the reticuloendothelial system and competed with MPC for uptake by the reticuloendothelial system cells, thereby resulting in increased plasma levels of MPC which in turn resulted in greater killing of the target cells. (Author abstract) (23 Refs)

18. ANTITUMOR ACTIVITY OF THE 3'-CHLOROETHYLNITROSOUREA ANALOG OF THYMIDINE AND THE PREVENTION BY COADMINISTERED THYMIDINE OF LETHALITY BUT NOT OF ANTICANCER ACTIVITY.

Lin TS, Fischer PH, Marsh JC, Prusoff WH
Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Cancer Res; 42(5):1624-1629 1982

The effect of the 3'-nitrosourea analog of thymidine (3'-[3-(2-chloroethyl)-3-nitrosoureido]-3' deoxythymidine; 3'-CTNU) on the growth of the murine L1210 and P388 leukemias in mice was investigated. A single injection of 3'-CTNU (40 mg/kg) was minimally toxic to mice bearing the L1210 leukemia and produced 60-day survivors. The coadministration of thymidine did not prevent the initial loss of wt caused by 3'-CTNU but did prevent the lethality otherwise produced in non-tumor-bearing mice. A single dose of thymidine (2 g/kg) administered to L1210-bearing mice had no anticancer activity and when coadministered with 3'-CTNU had no detrimental effect on the potent antitumor effects of 3'-CTNU. Similar results were obtained against P388 leukemia. The hematopoietic toxicity produced by the administration of 3'-CTNU to non-tumor-bearing mice, as evidenced by changes in the white blood cells, neutrophil, and agar diffusion chamber precursor cell concentrations in the hematocrit and in bone marrow cellularity, could not be prevented by thymidine. Therefore, the lethality produced by 3'-CTNU is probably not related to hematopoietic toxicity since the coadministration of thymidine completely prevented any lethality. (Author abstract) (40 Refs)

19. MECHANISM OF ACTION OF RADIOSENSITIZING COMPOUNDS WITH SIMILAR ELECTRON AFFINITY.

Gazso L
Orszagos 'Frederic Joliot-Curie' Sugarbiologiai', Sugaregeszsegugyi Kutato Intezet, Budapest, Hungary
Magy Onkol; 26(1):36-44 1982

Radiosensitizing compounds with similar electron activity and their possible mechanism of action are reviewed. 5-Nitro and 2-nitro-substituted nitroimidazole derivatives (metronidazole, 2-nitroimidazole and misonidazole) are the most promising radiosensitizing compounds with similar electron activity. Their action is probably based on an increase in the number of free radicals due to electron capture. (37 Refs) (In HUN)

20. INTERACTION BETWEEN HEPARIN AND ADRIAMYCIN IN MICE BEARING THE LEWIS LUNG CARCINOMA.

Colombo T, Delaini F, Ferrari R, Donati MB, Donelli MG, Poggi A
Istituto di Ricerche Farmacologiche, Mario Negri, Via Eritrea 62, 20157 Milan, Italy
Biomedicine; 34(3):124-128 1981

This investigation was prompted by the observation that adriamycin can interact with heparin in vitro and reduce its anticoagulant activity in in vivo tests in humans. The possible interactions between these two drugs were studied in C57Bl/6J mice bearing the Lewis lung carcinoma (3LL). The anticoagulant activity of heparin was temporarily reduced by concomitant treatment with adriamycin, as indicated by both activated partial thromboplastin times and blood recalcification times. In contrast, no changes were found in the kinetics of adriamycin disappearance from blood and accumulation in tissues if mice had been pretreated with heparin. Moreover, the effect of adriamycin on tumor and metastasis growth was unchanged by the association with the anticoagulant. These data indicate that the short-lived interaction between adriamycin and heparin, which can be documented by coagulation tests, does not necessarily involve a modification in the anticancer activity of the anthracycline. (Author abstract) (12 Refs)

21. FACTORS DETERMINING THE EFFECTIVENESS OF HYPOXIC CELL RADIOSENSITIZERS.

Vynskaya NP, Vygodskaya AL, Zharkov SA, Yarmonenko SP
All-Union Oncologic Scientific Center, Moscow M-478, USSR
Stud Biophys; 86(1):49-50 1981

Data on the relationship between irradiation conditions (acute or prolonged hypoxia) and the radiomodifying effectiveness of metronidazole (MNZ) are presented. MNZ was injected at the beginning of prolonged (20 min) or 20 min before acute (1 min) hypoxia in mice. A considerable radiosensitizing effect was observed at acute hypoxia. The absence of radiosensitizing effect in prolonged hypoxia could be explained by the increase in PO2 in critical systems such as stem cell populations caused by adaptation to hypoxic conditions and/or the MNZ injection which affected drug absorption and metabolism. Evidence supporting the former explanation is presented. (5 Refs)

22. SELECTIVE ENHANCEMENT OF BLEOMYCIN CYTOTOXICITY BY LOCAL ANESTHETICS.

Mizuno S, Ishida A
Dept. Antibiotics, Natl. Inst. Health, 2-10-35, Kamiosaki, Shinagawa-ku, Tokyo 141, Japan
Biochem Biophys Res Commun; 105(2):425-431 1982

The effect of local anesthetics on the response of cultured FM3A mouse mammary carcinoma cells to bleomycin cytotoxicity was investigated. Dibucaine markedly enhanced the bleomycin cytotoxicity in a dose dependent manner.The decrease in the survival of cells treated with graded doses of bleomycin with a fixed concentration of dibucaine was dependent on the dose of bleomycin. Procaine, lidocaine, butacaine, and tetracaine also greatly potentiated the cytotoxic activity of bleomycin. Dibucaine showed the strongest potentiating activity of all 5 anesthetics tested, and the potency of each compound to enhance the cytotoxicity was correlated to its anesthetic potency. Exposure of FM3A cells to dibucaine before treatment with bleomycin produced a similar enhancement of bleomycin cytotoxicity. This effect was maintained when bleomycin was added immediately following dibucaine treatment, and decreased as the time interval between anesthetic and bleomycin treatment increased. Dibucaine did not show the enhancement effect with either adriamycin, mitomycin C, or cisplatin, indicating that the anesthetics selectively potentiate bleomycin cytotoxicity. These results may be interpreted as a membrane phenomenon, in which the local anesthetics interact with the membrane lipids, modifying the membrane properties and resulting in an increased transport of bleomycin into the cell or a decreased efflux once it has entered the cell. (19 Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

23. ENZYMATIC RELEASE OF NITRIC OXIDE FROM L-ALANOSINE, AN ANTINEOPLASTIC ANTIBIOTIC.

Alston TA, Bright H
Dept. Biochemistry and Biophysics, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Biochem Biophys Res Commun; 105(2):560-566 1982

L-Alanosine, an antineoplastic antibiotic produced by Streptomyces alanosinicus, is a isonitramino analog of L-aspartic acid. L-Alanosine is metabolized in animals to the corresponding 2-oxo acid. It is suggested that the oxo acid undergoes nonenzymatic decomposition to produce reactive free radicals including nitric oxide. To the test this hypothesis, the 2-oxo acid was generated in vitro by the reaction of L-amino acid oxidase, isolated from Crotalus adamanteus venom, with L-alanosine. The reaction mixture included ferricytochrome c to detect one-electron donating reductants, and indication of the presence of nitric oxide. The mixture also included a diazo coupling assay for determining diazotization of sulfanilamide by inorganic nitrite, which might be produced by autoxidation and disproportionation of nitric oxide. The enzymatic oxidation of L-alanosine produced products capable of reducing ferricytochrome c, and diazotizing sulfanilamide. The results confirm the hypothesis that the oxo acid derived from L-alanosine decomposes into nitric oxide and other reactive free radical species. These products are highly reactive with a number of cellular constituents and may account for the cytotoxicity of L-alanosine. (24 Refs)

24. EFFECT OF LEVORIN ON ACTIVITY OF DIFFUSION PROCESSES IN MURINE EHRLICH'S CARCINOMA CELLS.

Lishnevskaia EB, Gorozhankina IS, Tereshin IM
All-Union Res. Technological Inst. Medicinal Antibiotics and Enzymes, Leningrad, USSR
Antibiotiki; 27(2):141-144 1982

The effect of polyene antibiotic levorin on the biological transport was studied in cultured cells of murine Ehrlich's carcinoma. Incubation of tumor cells with levorin at 0.25 ug/ml inhibited the active transport of amino acids. Levorin did not affect the transport of nucleosides or the penetration of cyclophosphamide. (17 Refs) (In RUS)

25. UPTAKE, EFFLUX, AND HYDROLYSIS OF ACLACINOMYCIN A IN FRIEND LEUKEMIA CELLS.

Fourcade A, Farhi JJ, Bennoun M, Tapiero H
(c/o Tapiero) Dept. Pharmacologie Cellulaire, Institut de Cancerlogie et d'Immunogenetique (INSERM U-50), Unite Simone et Cino del Duca de Pharmacologie Humaine des Cancers, 94804 Villejuif, France
Cancer Res; 42(5):1950-1954 1982

The kinetics of uptake by cells and nuclear incorporation of aclacinomycin A was studied in Friend leukemia cells. It was shown that uptake is a very rapid process. The intracellular concentration is maximum in 10 min and mainly (about 75%) localized in the nucleus. Most of the incorporated drug will disappear from the cell by a two-step mechanism: (a) efflux from the nucleus to the cytoplasm; and (b) deglycosidation at C-7 to the alkavinone form in the cytoplasmic fraction. The cellular uptake was temperature dependent but was not prevented by sodium azide treatment. We assumed, therefore, that it is related to the composition and to the dynamic structure of the cell surface membrane. Nuclear outward transport and deglycosidation were inhibited by sodium azide and low temperatures; this suggests that they are regulated by an active transport process and by an enzymatic activity, respectively. (Author abstract) (21 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

26. EFFECT OF ERGOT ALKALOIDS ON GROWTH OF MAMMARY GLAND CANCER IN MICE AND RATS.

Lagova ND, Ird EA, Chernov VA
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(1):73-74,76 1982

The antitumor efficacy of synthesized ergot alkaloids (EA) was studied in random-bred rats and CBA mice with transplanted mammary gland carcinoma. Of four EA tested, D-6-methyl-8-cyanomethylergolin alone reduced the yield of multiple breast tumors but did not affect the av latent period of tumor development. (8 Refs) (In RUS)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

27. ISOLATION AND CHARACTERIZATION OF A CHLAMYDOMONAS L-ASPARAGINASE.

Paul JH
Environmental Sciences Div., Code 4354, Naval Res. Lab., Washington, DC, 20375
Biochem J; 203(1):109-115 1982

An L-asparaginase (EC 3.5.1.1) specific for L-asparagine has been purified from a marine Chlamydomonas species, the first such enzyme to be purified from a microalga. The purified enzyme (mol wt 275,000) possessed a Km for asparagine of 1.34 x 10(-4) M and showed limited antitumor activity in an antilymphoma assay in vivo. Properties of the enzyme are contrasted with those of asparaginases from prokaryotic and eukaryotic sources. (Author abstract) (32 Refs)

INTERFERON AND OTHER ANTIVIRALS

28. GENETIC ANALYSIS OF THE ROLE OF CAMP IN MEDIATING EFFECTS OF INTERFERON.

Schneck J, Rager-Zisman B, Rosen OM, Bloom BR
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Proc Natl Acad Sci USA; 79(6,part1):1879-1883 1982

The effects of interferon (IFN) on Fc receptor-mediated phagocytosis, intracellular cAMP levels, antiviral activity, and growth inhibition were analyzed in a cloned macrophage-like cell line, J774.2, and variants derived from it. Purified IFN increased Fc receptor-mediated phagocytosis in J774.2 cells, and in cAMP-responsive nonphagocytic variants but was without effect in cAMP-unresponsive nonphagocytic variants, in adenylate cyclase-deficient variants, and in cAMP-dependent protein kinase-deficient variants. Under conditions in which IFN augmented phagocytosis, it increased intracellular levels of cAMP. Parental cells were highly sensitive to IFN-mediated growth inhibition. In contrast, cAMP-dependent protein kinase-deficient variants were only 1/100th as sensitive to growth inhibition by IFN. All cell lines tested, both responsive and unresponsive to cAMP, were equally protected by IFN against infection with vesicular stomatitis virus, demonstrating that the antiviral state was independent of cAMP. These results indicate that, in transformed macrophages, stimulation of phagocytosis and inhibition of growth by IFN are mediated through intracellular cAMP, whereas the antiviral state induced by IFN is independent of cAMP. (Author abstract) (31 Refs)

29. THE IDENTITY OF INTERFERON-BETA1 MRNA TRANSCRIPTS IN HUMAN FIBROBLASTS AND NAMALVA CELLS.

Gross G, Bruns W, Mayr W, Collins J
Abt. Genetik, Gesellschaft fur Biotechnologische Forschung mbH, Mascheroder Weg, 3300 Braunschweig, W. Germany

FEBS Lett; 139(2):201-204 1982

The messenger RNA (mRNA) for interferon-beta1 (IFN-b1) induced in different cell types by different modes of induction were compared. Synthesis of mRNA for IFN-b1 production was induced in human fibroblast cultures by exposure to cyclohexamide (50 ug/ml) and polyriboinosinic-polyribocytidylic acid (50 ug/ml). Synthesis of mRNA for IFN-b1 was induced in lymphoblastoid Namalva cells by exposure to Sendai virus for 5 hr. The DNA fragment EcoRI-F, which contains the entire IFN-b1 gene was used for S1 mapping. Klenow polymerase was used for 3'-end labeling. T4 DNA kinase was used for 5'-end labeling. Denaturing on 2% agarose gel indicated that IFN-b1 produced by the human fibroblasts was the same size as IFN-b1 produced by Namalva cells. Mapping studies indicated that mRNA for IFN-b1 induced by either system was 840 nucleotides in length without the poly(A) tail. The 5'-end labeled BglII fragment gave rise to a 640 nucleotide fragment; the 3'-end labeled fragment BglII fragment gave rise to a 200 base-pair fragment that was protected against S1-digestion. Results indicate that mRNA for IFN-b1 induced in different cell types by different induction systems can be of identical size. (15 Refs)

30. ALPHA INTERFERON AND ACYCLOVIR TREATMENT OF HERPES SIMPLEX VIRUS IN LYMPHOID CELL CULTURES.

Hammer SM, Kaplan JC, Lowe BR, Hirsch MS
Infectious Disease Unit, Dept. Medicine, Massachusetts General Hosp., Boston, MA, 02114

Antimicrob Agents Chemother; 21(4):634-640 1982

The T-lymphoblastoid cell line CEM, persistently infected with herpes simplex virus type 1, has been used to examine the antiviral efficacy of human alpha interferon and acyclovir, both alone and in combination. Acyclovir and interferon each produced dose-dependent decreases in virus titer at concentration ranges of 1 to 100 uM (approx 0.225 to 22.5 ug/ml) and 10 to 10,000 U/ml, respectively. Mean reductions in titer of 1.9 and 4.2 log10 PFU/ml were observed with 100 uM acyclovir and 10,000 U of interferon per ml, respectively, on day 10 of treatment. The combination of 100 uM acyclovir and 10,000 U of interferon per ml produced the most rapid fall in virus titer of all regimens examined and elimination of infectious virus by day 7. Prolonged treatment (greater than 10 days) with acyclovir or alpha interferon was accompanied by a gradual return of virus titer to control levels despite the continuous presence of drug. Virus preparations isolated from such cultures were tested for antiviral agent sensitivity by a plaque reduction method. Acyclovir-exposed isolates were found to be acyclovir resistant, with 50% inhibitory doses of greater than 200 uM, and to be thymidine kinase deficient. Alpha interferon-exposed isolates were not interferon resistant. These results suggest that, in persistently herpes simplex virus-infected CEM cells: (i) combination treatment with 100 uM acyclovir and 10,000 U of alpha interferon per ml is more effective in reducing virus titer than either agent alone; (ii) prolonged exposure to drug may result in development of resistance by either the virus strain or the host cell system; and (iii) development of acyclovir resistance by herpes simplex virus in lymphoid cells is mediated by thymidine kinase. (Author abstract) (37 Refs)

31. EFFECT OF MOUSE INTERFERON ON CELL TRANSFORMATION AND VIRUS PRODUCTION IN RAT CELLS EXOGENOUSLY INFECTED WITH MOLONEY MURINE SARCOMA AND LEUKEMIA VIRUSES.

Huleihel M, Aboud M
Microbiology and Immunology Unit, Faculty Health Sciences, Ben Gurion Univ. Negev, Beer Sheva, Israel

Int J Cancer; 29(4):471-476 1982

Foci of transformed cells, produced by MSV(124), appeared to result only from the primary infection, since this virus stock yielded a virus-nonproducing infection. On the other hand, the majority of foci scored in MSV/MLV-infected cultures, were generated by multiple secondary infections with the progenies of the primary infection. Mouse interferon (IF) was highly inhibitory for cell transformation by both virus stocks. However, this inhibition was apparent in MSV(124) infected cultures only if IF was added at least 12 hr before infection, whereas in MSV/MLV-infected cultures IF was highly effective even if added 24 hr after infection. The inhibition of focus formation by MSV(124) was irreversible after removal of IF, suggesting that IF inhibited an early step before provirus integration into the host genome. By contrast, in MSV/MLV-infected cultures focus formation was almost completely restored after recovery from the IF effect. Nevertheless, examination of virus production after IF removal proved that in MSV/MLV infection, too IF exerted an inhibitory effect before provirus integration. (Author abstract) (38 Refs)

32. THE EFFECT OF HYPERTONIC SALT ON INTERFERON AND INTERFERON MRNA SYNTHESIS IN HUMAN MG63 CELLS.

Meager A, Shuttleworth J, Just MD, Boseley P, Morser J
Div. Viral Products, Natl. Inst. Biological Standards and Control, Holly Hill Hampstead, London NW3 6RB, England

J Gen Virol; 59(part1):177-181 1982

After infection with Sendai virus or Newcastle disease virus (NDV) Strain F, human osteosarcoma MG63 cells produced large amounts of interferon-beta. Both interferon production and overall protein synthesis was strongly inhibited by hypertonic salt. Interferon mRNA synthesis, however, was little affected by hypertonic salt up to twice normal salt concentrations, although cellular RNA synthesis was inhibited under these conditions. The results are compared to those obtained with polyriboinosinic acid:polyribocytidylic acid copolymer [poly(rI)-poly(rC)] inductions of MG63 cells. (Author abstract) (14 Refs)

33. CELL GROWTH REGULATION DURING DENSITY INHIBITION AND INTERFERON TREATMENT.

Leandersson T, Lundgren E
Lab. Cell and Tissue Culture Res., Univ. Umea, S-901 87 Umea, Sweden

Exp Cell Res; 138(1):167-174 1982

The growth of P3HR-1, a Burkitt's lymphoma cell line, was regulated differently at high cell numbers and upon treatment with human leukocyte interferon (IFN-alpha). At terminal cell titer, cell growth was reduced by progressing through the cell cycle more slowly, whereas IFN-treated cells escaped from the cell cycle by going into a G0-like state. Furthermore, in comparison with density-inhibited cells, IFN-treated cells had, upon dilution into fresh medium, a longer lag period before they began to grow exponentially again. No G0/G1 restriction point was apparent in this cell line. These cells had to undergo one mitotic division before any IFN-induced inhibition of proliferation could be observed. (Author abstract) (19 Refs)

34. MICROTUBULE-DEPOLYMERIZING AGENTS INHIBIT MOLONEY MURINE LEUKAEMIA VIRUS PRODUCTION.

Satake M, Luftig RB
Dept. Microbiology and Immunology, Univ. South Carolina Sch. Medicine, Columbia, SC, 29208
J Gen Virol; 58(part2):339-349 1982

The effects of microtubule-depolymerizing agents on virion production in MJD-54 cells chronically infected with Moloney murine leukemia virus were examined. By measuring the amount of reverse transcriptase activity remaining in particles recovered from culture fluids, we found that incubation with 1 uM- or 10 uM-colchicine, vinblastine or nocodazole resulted in 30 to 40% decreases in virus production. The decrease in virus production did not seem to be due to general damage to the cells since cellular RNA and protein synthesis were only slightly, if at all, inhibited by the drug treatment (less than 10%). Furthermore, virus proteins accumulated inside drug-treated cells, viz, [35S]methionine-labeled Pr65gag showed a 1.5-fold increase over a 3 hr continuous label interval. Consistent with this accumulation of virus protein, electron microscope studies showed that inside drug-treated cells there was a 2-to 2.5-fold accumulation of virions within cytoplasmic vesicles. All of these results support the idea that cytoplasmic microtubules play a role in the production of murine leukemia virus. (Author abstract) (28 Refs)

35. EFFECT OF INTERFERON ON THE EXOGENOUS FRIEND MURINE LEUKEMIA VIRUS INFECTION.

Riggin CH, Pitha PM
(c/o Pitha), Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21218
Virology; 118(1):202-213 1982

Interferon treatment (600 U/ml) of NIH/3T3 cells induced greater than 90% reduction in the de novo production of Friend MuLV when measured 24 hr postinfection. Early events in viral replication such as the synthesis of proviral DNA and its subsequent integration into the cell genome were not inhibited by interferon treatment indicating that the suppression of virus production by interferon appears to occur after synthesis of proviral DNA. Analysis of viral RNA species present in controls and interferon-treated cells 24 hr after infection show that the same RNA species were present in the presence and absence of interferon. Synthesis of viral polypeptides was reduced but not blocked in interferon-treated cells when measured within 24 hr after infection while processing of gag precursor, Pr65gag, and glycoprotein precursor, gPr85env, to viral proteins was not altered. Phosphorylation of viral protein p12 but not that of the precursor, Pr65gag, was inhibited in newly infected interferon-treated cells. In contrast to the first replicative cycle, interferon did not inhibit synthesis of viral proteins, and phosphorylation of p12 in those cells chronically infected with F-MuLV. (Author abstract) (32 Refs)

36. LACK OF EFFICACY OF 2-DEOXY-D-GLUCOSE IN THE TREATMENT OF EXPERIMENTAL HERPES GENITALIS IN GUINEA PIGS.

Shannon WM, Arnett G, Drennen DJ
Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL, 35255
Antimicrob Agents Chemother; 21(3):513-515 1982

Topical treatment of herpes genitalis in female guinea pigs with 2-deoxy-D-glucose in either agarose gels or miconazole nitrate ointment failed to prevent the development of genital lesions or to reduce the mean titers of recoverable virus in vaginal swabs from infected animals. In contrast, phosphonoacetic acid was therapeutically effective. (Author abstract) (15 Refs)

37. INVOLVEMENT OF THE KIDNEY IN CATABOLISM OF HUMAN LEUKOCYTE INTERFERON.

Bino T, Edery H, Gertler A, Rosenberg H
Israel Inst. Biological Res., Ness Ziona, Israel
J Gen Virol; 59(part1):39-45 1982

The metabolic fate of human leukocyte interferon (HuIFN-alpha) was studied after intravenous injection into rats and cynomolgus monkeys. At various intervals the animals were sacrificed and the HuIFN-alpha content determined in serum and various tissues. HuIFN-alpha quickly disappeared from the circulation and was found mainly in the kidneys, in which levels were at least 7-to 10-fold higher than in the liver, spleen, lung, heart, brain, and muscles. No interferon was detected in urine. Subcellular fractionation of kidney revealed that the mitochondrial-lysosomal fraction (15,000 g) had a high HuIFN-alpha content. It was also found that HuIFN-alpha was rapidly inactivated by two types of proteinases found in the lysosomal fractions of rat, monkey and human kidneys, with an optimal pH of 3 to 4. The inactivation was partially inhibited by either pepstatin or leupeptin. Inactivation was totally prevented by a mixture of both inhibitors. Since it is known that interferon is scantily excreted in urine, our findings suggest that the kidney serves as a main site for its degradation. (Author abstract) (20 Refs)

OTHER RELATED STUDIES

38. HUMAN LEUKAEMIA: WHAT NEXT?

Schofield R
Peterson Lab., Christie Hosp. and Holt Radium Inst., Withington, Manchester M20 9BX, England
J Cell Physiol; Suppl1:95-97 1982

Research in human leukemia is reviewed. The candidacy of a compound for trial as an antileukemic agent is invariably ultimately judged by its activity against a number of transplanted mouse tumors such as the L1210, B16 melanoma, and the Lewis lung carcinoma. In a few experiments, investigating the activity of closely related alkylating agents, different drugs with the same functional groups have been seen to to have strikingly different effects; busulfan and isopropylmethane sulfonate affect the hemopoietic populations totally differently. (9 Refs)

39. USE OF CYCLIC ADENOSINE-3'5'-MONOPHOSPHATE AND ITS ANALOGS IN CANCER CHEMOTHERAPY.

Riazanov EM
N. Petrov Res. Inst. Oncology, Leningrad, USSR
Eksp Onkol; 4(1):8-13 1982

Literature data pertaining to the applications of cyclic AMP (cAMP) and its analogs in experimental cancer chemotherapy are reviewed. Biological role of cAMP includes mediation of the proliferation and differentiation of normal and transformed cells. The content of cAMP in cultured tumor cells was shown

to be lower than that in the normal cells. In vivo studies showed an increase of cAMP content in the adrenal cortex adenomas and hyperplasias, as compared with the normal adrenals. In vitro studies indicated that cAMP and its analogs inhibited the growth of cultured cells. The normal cells were less sensitive to cAMP than the homologous normal cells. The degree of inhibition depended upon the histology of tumor cells and the activity of protein kinases (PK). Treatment with chlorambucil or melphalan enhanced the activity of PK and increased the content of cAMP in sensitive Walker's carcinosarcoma and HeLa cells. Carminomycin did not affect cAMP level in murine lymphoid leukemia cells. (71 Refs) (In RUS)

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Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. MOLECULAR MECHANISMS OF ACTIVITY OF HORMONE-LINKED CYTOSTATICS.

Belousova AK, Boguslavskaia OA, Bergol'ts VV, Shkodinskaia EN, Kurdiumova KN

All-Union Cancer Res. Center, Moscow, USSR

Eksp Onkol; 4(2):41-46 1982

The effect of steroid carrier on the alkylating activity of distrone (ester of chlorophenacyl and androgen) and phenthyrine (a derivative of thyronine) was studied in mice bearing ascites sarcoma 37. Analysis of single-stranded breaks and cross-links in DNA molecule showed that the alkylating activity of distrone was approx 10x lower than that of chlorphenacyl. Distrone caused marked and prolonged inhibition of 3H-androgen binding with chromatin from cells of the ventral prostate, while chlorophenacyl did not affect the nuclear acceptor sites. Phenthyrine caused a 40-70% inhibition of labeled triiodothyronine binding with cellular receptors. (30 Refs) (In RUS)

2. BIOCHEMICAL CHANGES IN EXPERIMENTAL RAT BRAIN TUMORS INDUCED BY ETHYLNITROSOUREA AND HUMAN GLIOMAS AFTER DIBUTYRYL CYCLIC AMP TREATMENT.

Shibata I, Matsumoto M, Nagasawa S, Seiki Y, Takezawa J

Dept. Neurosurgery, Toho Univ., Sch. Medicine, 6-11-1, Omori-nishi, Ota-ku, Tokyo 143, Japan

Neurol Med Chir (Tokyo); 22(1):1-6 1982

Previous reports have shown that dibutyryl 3',5'adenosine monophosphate (DBc-AMP) suppresses growth of actively dividing tumor cells, accelerates normalization of cellular metabolism and elevates the intracellular level of cyclic AMP. In an effort to study this mechanism further and define its significance, studies were performed on pregnant rats with ethylnitrosourea (ENU) induced gliomas and human subjects with malignant gliomas. RNA and DNA were detected in remarkably high concentrations in the tumor tissue with a significant reduction after treatment with DBc-AMP. The reduction was more pronounced with RNA. Free amino acids were noted in relatively low concentrations in tumor tissue. However, treatment with DBc-AMP resulted in a significant elevation of their value. The levels of glutamic acid, aspartic acid and GABA increased to levels corresponding to the composition of free amino acids in normal brain tissues. Lysosomal enzyme activity in tumor tissue was 10x greater than that in normal brain tissue. This activity dropped significantly after administration of DBc-AMP. In rats with ENU induced glioma, the uptake of radioactive [H3]DBc-AMP by tumor tissue occurred in a volume 2-3x that of normal tissue. However, the ratio of [H3]cyclic AMP/cyclic AMP was less than that in normal tissue, implying that an enhanced synthesis of endogenous cyclic AMP occurs after administration of DBc-AMP. (Author abstract) (22 Refs)

3. THE ORDER OF DNA REPLICATION IN MAMMALIAN CELLS. A MODIFIED DENSITY LABELLING PROCEDURE FOR ISOLATING SEQUENCES REPLICATED AT SPECIFIC TIMES.

Grady LJ, Sanders ML
Div. Lab. and Res., New York State Dept. Health, Albany, NY, 12201
Exp Cell Res; 138(2):480-485 1982

These experiments were directed towards establishing a procedure for isolation of the DNA sequences replicated at different times in S phase for further study. Primary considerations were thus for a method that gave fairly large quantities of cells as well synchronized in S phase as possible. The use of Chinese hamster ovary (CHO) cells synchronized by isoleucine starvation followed by exposure to hydroxyurea (1) seemed to be most promising and was explored in detail. During the course of this work, a labeling scheme was developed that involved exposure to BrdUrd during the same time window in two sequential S phases. Only those regions of the genome replicated in the same interval in each S period contained BrdUrd in both strands and these were readily isolated in CsCl gradients. As applied in the present experiments, this labeling procedure showed no untoward effects on cell-cycle traverse and gave DNA distributions in density gradients that closely approximated those that would be expected for the conditions employed. (Author abstract) (11 Refs)

4. MECHANISM OF ACTION OF ANTITUMOR 3-(2-HALOETHYL)ARYLTRIAZENES ON DEOXYRIBONUCLEIC ACID.

Lown JW, Singh R
Dept. Chemistry, Univ. Alberta, Edmonton T6G 2G2, Alberta, Canada
Biochem Pharmacol; 31(7):1257-1266 1982

A series of novel 3-(2-haloethyl)aryltriazenes, many of which exhibit marked antileukemic activity in animal test neoplasms, react readily with DNA under physiological conditions. With regard to a single strand scission (SSS), in contrast to the related 2-haloethylnitrosoureas which exhibit both Type I and Type II SSS (single strand scission) of DNA, the triazenes appear to react via Type II SSS of DNA by base alkylation followed by depurination or depyrimidination and subsequent hydrolysis of the apurinic site. The latter reaction was confirmed using apurinic site-specific endonuclease VI. A 3-(2-chloroethyl)aryltriazene readily degraded poly A by phosphate alkylation at a rate much faster than given by comparable nitrosoureas. Overall, the triazenes showed a preference for reaction at the more acidic phosphate sites in the DNA owing to their unique acid-promoted decomposition. This may, in part, account for the lack of detection of DNA interstrand crosslinks and indicates a fundamentally different mechanism of action of the 3-(2-haloethyl)triazenes from the 2-haloethylnitrosoureas. (Author abstract) (40 Refs)

5. REPAIR OF DNA INTERSTRAND CROSSLINKS AFTER BUSULPHAN. A POSSIBLE MODE OF RESISTANCE.

Bedford P, Fox BW
(c/o Fox) Paterson Lab., Christie Hosp. and Holt Radium Inst., Wilmslow Road, Withington, Manchester M20 9BX, England
Cancer Chemother Pharmacol; 8(1):3-7 1982

The technique of alkaline elution was used to study the interaction between busulfan (BS) and the DNA of cells derived from the transplantable rodent Yoshida sarcoma. The findings were related to the in vitro cytotoxicity and chromosome aberrations (CHA) in the anaphase of cell lines resistant (YR) and sensitive (YS) to BS are discussed. The doses of BS producing 50% cell death were 7.5 and 54.5 ug/ml for YS and YR, respectively. BS (50 ug/ml) treatment in both cell lines caused a greater than two-fold depression in the mitotic index after 24 hr post-treatment incubation. A four-fold greater number of CHA could be observed in the YS than the YR line. Typical elution profiles in YS cells after a single 1-hr dose of BS (100 ug/ml) are presented. A small but reproducible proteinase-resistant retention was observed immediately after BS treatment, indicating the presence of DNA interstrand cross-links. As the dose of BS was increased, an increasing filter retention was observed, from which the number of cross-links per unit DNA could be assessed. The relationship between drug dose and the frequency of DNA interstrand cross-links is shown. A temporal study of DNA interstrand cross-linking after a single dose of BS (50 ug/ml; 1 hr) revealed a gradual increase in cross-linking over the first 4 hr, followed by a disappearance over 24 hr in the YR line. In the YS line, an increase in cross-linking over 4 hr and very little loss was observed 24 hr after drug removal. The time-course of cross-linking in both lines in terms of the relative retention is shown. (19 Refs)

6. INTERCALATIVE BINDING OF 3-NITROBENZOTHIAZOLO (3,2-A) QUINOLINIUM SALT TO DNA (MEETING ABSTRACT)

Baez A, Gonzalez F
Department of Pharmacology, Medical Sciences Campus, UPR, Box 5067, San Juan, PR, 00936
Fed Proc; 41(3):1202 1982

NBQ (3-Nitrobenzothiazolo (3,2-a) quinolinium perchlorate) has been shown previously to exert strong cytostatic and antitumor activity. The deoxyribonucleic acid (DNA) binding characteristics of NBQ have been studied by UV-visible and fluorescence spectrophotometric, thermal denaturation and viscometric methods. Viscometric studies showed that NBQ increased the viscosity of sonicated rod-like DNA fragments. Binding parameters were determined by spectrophotometric studies. The results obtained are consistent with an intercalative binding model for the NBQ DNA interaction. (no Refs)

7. THE INTERACTION OF DAUNOMYCIN WITH CALF-THYMUS NUCLEOSOMES (MEETING ABSTRACT)

Chaires JB, Dattagupta N, Crothers DM
Department of Chemistry, Yale University, New Haven, CT, 06511
Fed Proc; 41(3):1201 1982

Daunomycin (DM) is an anthracycline antibiotic widely used in cancer chemotherapy. We have previously examined in detail the interaction of the drug with DNA, and report here the interaction of DM with 146 bp (base pairs) and 175 bp nucleosomes prepared from calf thymus. Relative to free DNA, DM binds to nucleosomes with a 10 fold lower affinity, although the total number of available binding sites is not dramatically changed. The salt dependence of DM binding to nucleosomes parallels that found for the interaction of the drug with DNA, with Z psi equals-0.84. Thermal denaturation studies on these nucleosomes in the absence of DM show the usual biphasic melting behavior; at low DM: DNA base pair ratios, the low temperature transition is preferentially stabilized, while the Tm of the main transition is unaltered. Sedimentation velocity, quasielastic light scattering, and transient electric dichroism experiments show that DM unfolds the nucleosome, leading to a 10% increase in the frictional coefficient. At high nucleosome concentration and/or high drug: base pair ratios, DM promotes nucleosome self-association. (no Refs)

8. EFFECTS OF ADRIAMYCIN ON HEART AND SKELETAL MUSCLE CHROMATIN.

Van Helden PD, Wiid IJ
M.R.C. Unit Molecular and Cellular Cardiology, Dept. Medical Physiology, and Biochemistry Univ. Stellenbosch Medical Sch., P.O. Box 63, Tygerberg 7505, South Africa
Biochem Pharmacol; 31(6):973-977 1982

Interactions between adriamycin (ADM) and chromatin from heart and skeletal muscle from 15 day-old chicken embryos were investigated. Adriamycin interacts with the DNA of chromatin and this interaction is modified by the chromatin proteins. One of the effects of this interaction is an increase in the melting temperature (Tm) of the DNA, where adriamycin is observed to increase the Tm of heart chromatin to a greater extent than skeletal muscle chromatin. Adriamycin also inhibits in vitro DNA and RNA synthesis in isolated chromatin and nuclei. This inhibition is observed to be greater in heart muscle. Inhibition of transcription in the myocardium could be a major cause of adriamycin-induced cardiomyopathy. (Author abstract) (37 Refs)

9. ADRIAMYCIN-INDUCED COMPACTION OF ISOLATED CHROMATIN.

Waldes H, Center MS
(c/o Center) Div. Biology, Kansas State Univ., Manhattan, KS, 66506
Biochem Pharmacol; 31(6):1057-1061 1982

Adriamycin and certain other agents such as daunomycin, rubidazone and 1,4-dihydroxyl-5,8 bis [[2-[(2-hydroxyethyl)amino]ethyl]amino]9,10 anthracenedione (DHAQ) were capable of inducing a considerable increase in the sedimentation rate of isolated chromatin. In contrast, N-trifluoroacetyl-adriamycin-14-valerate (AD-32) was without effect in this system. Electron microscope studies of chromatin incubated with adriamycin, rubidazone and DHAQ showed that all of these drugs were capable of inducing the formation of highly condensed DNA structures. When chromatin was treated with 0.4 M NaCl, its ability to serve as a substrate for adriamycin-induced compaction was abolished. However, the salt-treated chromatin could still be condensed by DHAQ and rubidazone. The results of this study, therefore, show that a variety of closely related antitumor agents are capable of condensing isolated chromatin. However, certain of these compounds had distinct substrate requirements for the compaction reaction. (Author abstract) (20 Refs)

10. QUANTITATIVE STUDIES ON BLEOMYCIN-INDUCED STRAND BREAKAGE OF CHROMATIN DNA.

Kataoka K
Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Okayama Igakkai Zasshi; 93(3/4):361-381 1981

Single and double strand breakage of DNA by bleomycin under various conditions was analyzed quantitatively using purified simian virus 40 (SV40) DNA and SV40 chromatin. The method employed for DNA assay was fluorometry of SV40 DNA separated into three forms I, II, and III by 1.4% agarose gel electrophoresis and stained with ethidium bromide. This method was extremely simple and accurate for quantitative estimation of single and double strand breakage of circular DNA. The amount of bleomycin required for in vitro breakage of SV40 chromatin DNA was much higher than that of naked SV40 DNA. 2-Mercaptoethanol accelerated bleomycin-induced DNA strand breakage. The concentration of 2-mercaptoethanol required for the acceleration was higher in SV40 chromatin than in SV40 DNA. DNA strand breakage was induced by ferrous ions in the absence of bleomycin to a similar level in SV40 chromatin and in SV40 DNA. The acceleration of bleomycin-induced strand breakage by a low concentration of ferrous ion was higher in SV40 DNA than in SV40 chromatin. Ethylenediamine tetraacetic acid (EDTA) and copper ions were not efficient for stopping the reaction of bleomycin-induced DNA breakage. Sodium dodecyl sulfate (SDS) was a useful reagent for stopping the reaction. (Author abstract) (75 Refs) (In JPN)

11. NONINTERCALATIVE DNA-BINDING ANTITUMOUR COMPOUNDS.

Baguley BC
Cancer Res. Lab., Univ. Auckland Medical Sch., Private Bag, Auckland, New Zealand
Mol Cell Biochem; 43(3):167-181 1982

A family of compounds which appear to bind reversibly to double stranded DNA without intercalation between DNA base pairs has been defined. Methods are described by which this non-intercalative binding can be characterized using ultraviolet spectrometry, fluorimetry with ethidium as a probe, viscometry and other hydrodynamic techniques, circular dichroism and nuclear magnetic resonance spectrometry. antibiotics which fall into this family include the antibiotics distamycin A, netropsin, mithramycin, chromomycin and olivomycin. Synthetic antitumor agents include diarylamidines such as berenil, phthalanilides, aromatic bisguanylhydrazones and bisquaternary ammonium heterocycles. A survey has been made of the general requirements of this family of compounds for DNA binding and biological activity. Binding of drugs to the minor groove of the DNA double helix appears to be the most likely mechanism for the antitumor action of these compounds (Author abstract) (91 Refs)

12. PLASMID R46-MEDIATED PROTECTION AGAINST BLEOMYCIN IS POLA+-DEPENDENT.

Attfield PV, Pinney RJ
Microbiology Section, Dept. Pharmaceutics, Sch. Pharmacy, Univ. London, Brunswick Square, London WC1N 1AX, England
J Gen Microbiol; 128(part3):539-547 1982

Strains of Escherichia coli deficient in post-replication recombination repair were more sensitive to bleomycin than wild-type, repair-proficient strains. Mutants lacking excision repair functions were no more sensitive to bleomycin than the wild-type strains, indicating that this pathway is not involved in the repair of bleomycin-damaged DNA. Plasmid R46 not only protected repair-proficient strains but also those with recB, recC, uvrA or lig genotypes, suggesting that R46 protection against bleomycin is independent of these host repair functions. However, R46 protection was abolished in recA or polA strains, indicating that these gene functions are necessary for plasmid-mediated protection. It is suggested that protection may be due to a recA+-dependent interaction of a plasmid-encoded product with host DNA polymerase I, resulting in an increase in the DNA repair capacity of cells. (Author abstract) (47 Refs)

13. GENETIC EFFECTS OF SOME PLATINUM CO-ORDINATION COMPLEXES ON E. COLI DNA AS REVEALED BY TRANSFORMATION STUDIES.

Hoekstra WP, Daemen CA, Otto ER
Dept. Molecular Cell Biology, State Univ. Utrecht, Padualaan 8, Utrecht 3584 CH, The Netherlands
Mutat Res; 94(1):53-62 1982

The genetic effects on Escherichia coli DNA of cis-diamminedichloroplatinum(II) (cisPt2), of its trans-isomer trans-PT2, and of cis-Pt(2.2-dimethyl-1,3-diaminopropane)Cl4 (cisPt4) are reported. Genetic analysis of transformants obtained with DNA treated by the various platinum complexes indicated that DNA lesions induced by cisPt2 and cisPt4 markedly influence genetic processing in recipient cells. No genetic effects were observed when trans-Pt2 was applied in similar concentrations. CisPt2 lesions appear to provide a stimulus for crossover events, while cisPt4 lesions lead to loss of linkage of genetic information in the donor DNA. The genetic effects of cisPt2 lesions in DNA were more pronounced in a uvrB recipient mutant than in a wild-type recipient, indicating that there is uptake of Pt-DNA and partial repair of Pt-induced lesions by the cellular excision repair system. The observation that transPt2 showed no effect when applied in similar concentrations at which cisPt2 gave significant effects may have relevance in terms of their differing efficacies as anti-neoplastic agents. (26 Refs)

14. INFLUENCE OF TEMPERATURE ON PLATINUM BINDING OF DNA, CELL KILLING, AND MUTATION INDUCTION IN ESCHERICHIA COLI K-12 CELLS TREATED WITH CIS-DIAMMINEDICHLOROPLATINUM(II).

Brouwer J, Fichtinger-Schepman AM, Van de Putte P, Reedijk J
Lab. Molecular Genetics, Wassenaarseweg 64, 2333 AL Leiden, The Netherlands
Cancer Res; 42(6):2416-2419 1982

Cell killing and specificity of mutation induction by treatment of Escherichia coli K-12 cells with cis-Pt(NH3)2Cl2 at various temperatures have been studied. Survival experiments show that the cell killing by cis-Pt(NH3)2Cl2 is enhanced with increasing temperature. This effect is explained by an increase in the amount of platinum bound to the DNA. The binding is the same in repair-proficient and in repair-deficient cells. However, the mutation induction in the lacI gene is much more strongly enhanced than could be expected from the increased platinum binding. This phenomenon is attributed to a different distribution of the induced lesions by cis-Pt(NH3)2Cl2 at various temperatures and not to an aberrant excision repair. Analysis of the induced lacI mutants revealed an increase in the percentage of nonsense mutants at higher temperature. Among the nonsense mutations, base-pair substitutions at GAG and particularly at GCG sequences are enhanced by the increasing temperature. The results are in agreement with our hypothesis that local denaturation of DNA, known to be promoted at higher temperature, is necessary for the formation of intrastrand cross-links at two guanine bases separated by a third base. (Author abstract) (10 Refs)

15. COMPARISON OF THE INTERACTION OF CIS- AND TRANS-DIAMMINEDICHLOROPLATINUM(II) WITH DNA BY A SIMPLE FILTER BINDING ASSAY.

Eastman A
Dept. Biochemistry, Univ. Vermont Coll. Medicine, Burlington, VT, 05405
Biochem Biophys Res Commun; 105(3):869-875 1982

While cis-diamminedichloroplatinum(II) (cisDDP) has been shown to be an effective chemotherapeutic agent against a variety of tumor types, its trans isomer is ineffective. Based upon a property of nitrocellulose filters to selectively retain DNA that contains single stranded regions, the abilities of the cis- and trans- isomers of DDP to bind to DNA were compared. While local denaturation of DNA was detected easily with the cis-isomer, local denaturation of DNA was not detectable with the trans isomer until much higher concentrations of the drug were used. DNA interstrand crosslinks were detectable at very low levels of trans-DDP; however, assuming that all of the platinum had reacted with DNA, it was calculated that 1/50 platinations form an interstrand crosslink (compared to 1/150 after cis-DDP). Their greater frequency than caused by cis-DDP is presumably due to the fact that, in the absence of intrastrand crosslinks, more monofunctional platinations are available to potentially form interstrand crosslinks. The rate of reaction between trans-DDP and DNA was slower than that for the cis-isomer, although maximum effect was observed by 24 hr. These results indicate major differences in the type of reaction between the two platinum analogues and DNA. Such differences are readily detected by the filter assay described. (12 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

16. PRONOUNCED INHIBITION OF CALMODULIN BY PLATINUM COMPLEXES (MEETING ABSTRACT)

Wallace RW, Schonbaum GR, Cheung WY
Department of Biochemistry, St Jude Children's Research Hospital, Memphis, TN, 38101
Fed Proc; 41(3):504 1982

It is known that cis-Diamminedichloroplatinum (II) (c-Pt), a compound with antineoplastic activity, is particularly effective for treatment of testicular and ovarian cancers. It is also promising in therapy of brain tumors. Its use, however, is limited by adverse effects, especially nephrotoxicity. Calmodulin (CaM) is present in high levels in testis and brain, mediating many of the effects of Ca++, which controls key cellular processes, including chromosome movement and cell division. We investigated the potential effect of c-Pt on CaM using phosphodiesterase to monitor its activity. c-Pt does not affect CaM activity; however, its 'aquo'-derivative is a potent inhibitor. The drug did not alter basal phosphodiesterase activity. Kinetic experiments showed that the 'aquo'-derivative at micromolar concentrations abolishes CaM activity within a few hours. Ca++ protects CaM from inactivation. Inhibition could be reversed by thiourea, 2,3-dimercaptopropane sulfonate and diethyldithiocarbamate. The drug-inactivated CaM did not show the characteristic Ca++-dependent conformational changes. The 'aquo'-derivative of trans-platinum is ineffective as an anti-neoplastic agent, but was equally potent in suppressing CaM activity. This suggests that CaM inhibition by c-Pt is not central to its antineoplastic activity; however, it may constitute a basis for drug toxicity. (no Refs)

17. EFFECTS OF ALL-TRANS-RETINOIC ACID (RETINOIC ACID) AND 4-HYDROXYPHENYLRETINAMIDE ON SYNOVIAL CELLS AND ARTICULAR CARTILAGE.

Brinckerhoff CE, Nagase H, Nagel JE, Harris ED
Dept. Medicine, Connective Tissue Disease Section, Darthmouth-Hitchcock Medical Center, Hanover, NH, 03755
J Am Acad Dermatol; 6(4,part2):591-602 1982

Monolayer cultures of rabbit synovial fibroblasts and explants of rabbit articular cartilage were exposed to naturally occurring all-trans-retinoic acid (RA: 0.03 or 0.3 ug/ml) or synthetic 4-hydroxyphenylretinamide (OHPRT: 0.03 or 0.3 ug/ml). In cultured fibroblasts, phorbol myristate acetate (PMA: 10(-8) M) induced colagenase (Case) synthesis that was inhibited by RA (0.3 ug/ml, dexamethasone (10(-7) M)) or PMA. Exposure to combinations of RA and prednisolone (10(-10) M) caused additive inhibition of Case production. OHPRT prevented PMA-induced increases in prostaglandin E2 (PGE2) production, but RA did not. Both RA and OHPRT enhanced the increased levels of plasminogen activator observed in PMA-exposed cells. In articular cartilage explants, 40% of the total glycosaminoglycan (GAG) content was released from control or OHPRT-exposed explants; RA exposure induced the release of 80% of the total GAG (a measure of potential toxicity). OHPRT inhibited Case and PGE2 production by rabbit synovial fibroblasts, but was not toxic to explanted articular cartilage. These findings suggest that retinoids are generally toxic to chondrocytes and therefore should not be considered as potential therapeutic agents, although retinoids have been used successfully in cancer chemotherapy and in the treatment of several skin diseases. Further research is needed to assess the possible role of retinoids in controlling the production of the mediators of joint destruction in rheumatoid diseases (Case, PGE2, and plasminogen activator). (65 Refs)

18. EFFECT OF RETINOIC ACID PRETREATMENT ON 12-O-TETRADECANOYLPHORBOL-13-ACETATE-INDUCED CELL POPULATION KINETICS AND POLYAMINE BIOSYNTHESIS IN HAIRLESS MOUSE EPIDERMIS.

Astrup EG, Paulsen JE
Inst. Pathology, Univ. Oslo, Rikshospitalet, Natl. Hosp., Oslo 1, Norway
Carcinogenesis; 3(3):313-320 1982

A single topical application of 17 nmol 12-O-tetradecanoylphorbol-13-acetate (TPA) to the skin of hairless mice induces characteristic transient alterations in the epidermal cell turnover and maturation (0-96 hr), associated in time with characteristic changes in the activities of L-ornithine carboxy-lyase (EC 4.1.1.17) (ODC) and S-adenosyl-L-methionine carboxy-lyase (EC 4.1.1.50) (SAM-D) and in the accumulation of polyamines. The effects on these responses of local pretreatment of the skin with retinoic acid 1 hr prior to TPA were investigated at selected time points. Retinoic acid inhibited the TPA-induced ODC activity and the ensuing accumulation of putrescine, but did not alter the TPA-induced SAM-D activity or the molar ratio of spermidine/spermine. This pretreatment also decreased the number of dividing basal cells in the first TPA-induced synchronized wave of proliferating cells. However, during the subsequent period of proliferation, the number of dividing cells in the retinoic acid pretreated group was comparatively increased. Hence, at four dose levels of retinoic acid (0.17, 1.70, 17.0 and 170 nmol), which all inhibited the TPA-induced ODC effectively, there was no change in the total number of basal cells that divided during 16-48 hr after TPA-application. The theory is put forward that retinoic acid might exert its antitumorigenic effect during tumor promotion with TPA by interfering with the rate and/or quality of epidermal cell maturation, rather than by inhibiting cell proliferation. (Author abstract) (62 Refs)

19. THE INHIBITION OF DNA REPAIR BY APHIDICOLIN OR CYTOSINE ARABINOSIDE IN X-IRRADIATED NORMAL AND XERODERMA PIGMENTOSUM FIBROBLASTS.

Waters R, Crocombe K, Mirzayans R
Genetics Dept., Univ. Coll., Singleton Park, Swansea SA2 8PP, England
Mutat Res; 94(1):229-234 1982

By incubating x-irradiated human fibroblasts with or without aphidicolin (APC) or cytosine arabinoside (AraC), it was investigated (1) whether DNA polymerase alpha participates in the repair of x-ray-induced DNA damage in normal and xeroderma pigmentosum (XP) cells incapable of excising UV-induced pyrimidine dimers, and (2) whether any responses seen with APC are observed with AraC, a known inhibitor of DNA replication and DNA repair in mammalian cells. Normal fibroblasts and excision-deficient XP fibroblasts were prelabeled with [14C]- and [H3]thymidine, respectively, They were then plated in the same dishes and exposed to a range of x-ray doses prior to incubation with or without either APC or AraC. DNA was then isolated on alkaline sucrose gradients. Profiles of gradients indicated that after doses of 150 or 250 Grays the repair of a fraction of the DNA damage was inhibited in both normal and XP cells by APC or AraC. Incubations with both AraC and APC did not increase the breaks seen with either agent alone. The response to post-irradiation incubation with APC was very similar to that seen with AraC, which was also seen after UV-irradiation. It was suggested that AraC blocks both semi-conservative replication and repair replication in a way similar to that of APC, ie, by blocking DNA polymerase alpha. (12 Refs)

20. STEM CELL (CFUS) PROLIFERATION INHIBITOR IN BLOOD OF MICE INJECTED WITH HYDROXYUREA.

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Dept. Pathophysiology, Charles Univ., U Nemocnice 5, 128 53 Praha 2, Czechoslovakia
Cell Tissue Kinet; 15(3):263-268 1982

Analysis of the mouse hemopoietic stem cell (CFUs) kinetics after hydroxyurea administration has provided an in vivo assay suitable for detection of factors which inhibit recruitment of non-proliferating G0-CFUs into cell cycle, or transit of CFU's through the G1 phase. Using this assay, it has been demonstrated that plasma obtained from mice which had received hydroxyurea approx 12-14 hr previously, possesses a factor which inhibited the triggering of CFUs into the cell cycle. The appearance of this CFUs proliferation inhibitor occurred at a time when 60-70% of the CFUs were synchronized in the S phase of the cell cycle, as a consequence of hydroxyurea action. Some basic properties of the inhibitor were investigated. (Author abstract) (10 Refs)

21. PARTICIPATION OF POLY(ADP-RIBOSYL)ATION IN THE DEPRESSION OF RNA SYNTHESIS CAUSED BY TREATMENT OF MOUSE LYMPHOMA CELLS WITH METHYLNITROSOUREA.

Taniguchi T, Agemori M, Kameshita I, Nishikimi M, Shizuta Y
Dept. Medical Chemistry, Kochi Medical Sch., Kochi 781-51, Japan
J Biol Chem; 257(8):4027-4030 1982

When mouse lymphoma cells (L-1210) are treated with methylnitrosourea, a DNA-damaging agent, polyadenosine diphosphoribose (poly(ADP-ribose)) synthetase activity increases five to eight-fold in 2-3 hr, while RNA polymerase activity remains constant for an initial 2 hr and then gradually decreases to 25-30% of the control level in 5 hr. Both alpha-amanitin-sensitive and -resistant RNA polymerase activities are depressed to the same degree by the treatment with methylnitrosourea. The depression in RNA synthesis is virtually prevented when the treated cells are cultured in the presence of 3-aminobenzamide, a specific inhibitor of poly(ADP-ribose) synthetase. Analyses of the RNA extracted from the cells labeled with [3H]uridine by agarose gel electrophoresis and by poly(U)-Sepharose column chromatography show that the contents of ribosomal precursor RNA and poly(A)-containing RNA are both low in the methylnitrosourea-treated cells as compared with those in the untreated cells and that the reduction in the contents of these kinds of RNA is almost completely prevented by the addition of 3-aminobenzamide to the culture medium. These results suggest that the enhancement of poly(ADP-ribosyl)ation causes the decrease in both synthesis of ribosomal RNA and messenger RNA. (Author abstract) (36 Refs)

22. MECHANISMS OF ACTIONS OF NEOCARZINOSTATIN (NCS) AND NCS-ASSOCIATED NONPROTEIN CHROMOPHORE.

Ohtsuki K, Ishida N
Dept. Bacteriology, Tohoku Univ. Sch. Medicine, Sendai, Japan
Tanpakushitsu Kakusan Koso; 26(7):937-949 1981

An antitumor antibiotic, neocarzinostatin (NCS), isolated from the culture of Streptomyces carzinostatics is widely used for the therapy of gastric, pancreatic, and bladder cancers and of acute leukemia. The main biological activity of NCS is to inhibit DNA synthesis by cutting the nucleotide chain. Other biological activity, such as the inhibitory effect in G2 phase are discussed. The biological specificity of NCS was presented in comparison with other antibiotics, such as bleomycin, and mitomycin. (74 Refs) (In JPN)

23. A 'HEXOKINASE EFFECT' IN THE INHIBITION OF OXIDATIVE PHOSPHORYLATION IN HEART MUSCLE MITOCHONDRIA BY ADRIAMYCIN.

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Dept. Biochemistry, Indian Inst. Science, Bangalore 560 012, India
Biochem Biophys Res Commun; 105(4):1440-1445 1982

The effect of hexokinase (HEX) on the inhibitory action of adriamycin (ADR) on succinate-dependent oxidative phosphorylation (OP) in mitochondria from the liver, kidney, and heart of adult albino rats was studied. Oxidative phosphorylation was measured manometrically and polarographically. With the manometric method, substrate oxidation and coupled phosphorylation by freshly isolated heart muscle mitochondria were progressively inhibited with increasing concentrations of ADR. With succinate used as a substrate, OP was inhibited 50% with only 5 uM ADR, while 100-fold and 300-fold higher concentrations were necessary for equivalent inhibition when pyruvate plus malate or ascorbate plus N,N,N',N',-tetramethyl-p-phenylene-diamine were used as the substrate. The polarographic method did not demonstrate such high sensitivity. The major difference between the two assays was the use of the HEX trap for the recycling of ADP in the manometric method. Addition of HEX to the reaction medium in the polarographic method drastically enhanced the inhibitor potency of ADR towards succinate oxidation. In the presence of HEX, only 27 +-8 uM ADR was needed for 50% inhibition of State 3 oxidation in the presence of HEX. Further results demonstrated that the energized state of the membrane was involved in eliciting the 'HEX effect' and that ADR may have low permeability across the inner mitochondrial membrane. The 'HEX effect' was not observed when liver or kidney mitochondria were used. These findings suggest a biochemical explanation for the extreme cardiac toxicity of ADR. (15 Refs)

24. BASIS FOR THE DIFFERENTIAL ACTION OF AMINONUCLEOSIDE ON NORMAL AND TRANSFORMED HUMAN FIBROBLASTS.

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JNCI; 68(3):407-413 1982

Acid-soluble extracts of normal human fibroblasts (IMR 90 cells) exposed to [3H]aminonucleoside of puromycin ([3H]AMS) contained larger amounts of unchanged AMS than did similar extracts of their transformed counterparts (AG 2804 cells). The radioactive compounds present in IMR 90 cells were further analyzed by sequential high-voltage paper electrophoresis, enzyme digestion, and paper chromatography. In addition to unchanged [3H]AMS, only [3H]adenosine, [3H]inosine, and [3H]adenosine monophosphate could be detected, apparently derived from [3H]adenosine present in the [3H]AMS samples added to the cultures. Consistent with the absence of metabolism of AMS in IMR 90 cells was the failure to find AMS derivatives in the RNA or DNA of these cells. The content of ribonucleoside triphosphates (rNTPs) in acid-soluble extracts of IMR 90 cells was significantly reduced by AMS treatment, and nuclei or broken cell preparations obtained from AMS-treated IMR 90 cells incorporated [3H]UTP into macromolecules at approximately control rates, when supplemented with rNTPs. These findings indicated that the reduced level of rNTPs may be responsible for the AMS-induced inhibition of RNA synthesis in normal cells. (Author abstract) (23 Refs)

25. EFFECTS OF METHOTREXATE ON RIBONUCLEOTIDE POOLS IN GROWING AND IN GROWTH-ARRESTED TUMOR CELLS AND ANTAGONISM BY RNA SYNTHESIS INHIBITORS.

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J Biol Chem; 257(8):4279-4284 1982

We examined the mechanism of ribonucleotide pool changes in methotrexate-treated Ehrlich ascites tumor cells in culture. In exponentially growing cells, methotrexate inhibited ATP and GTP formation and stimulated UTP and CTP formation by the de novo pathways. Over the following 4 hr ATP and GTP decreased and UTP and CTP increased. During this period RNA synthesis rates decreased by 30 to 40%. Inhibitors of nucleolar RNA synthesis (actinomycin D, doxorubicin, or cycloheximide), but not of DNA synthesis (cytosine arabinoside), prevented ATP and GTP depletion. These results suggest that ATP and GTP were depleted in methotrexate-treated cells because the shift-down of RNA synthesis occurred more slowly than the inhibition of ATP and GTP supply. UTP and CTP pools increased because of increased de novo synthesis and because of decreased consumption in RNA synthesis. Ribonucleoside triphosphates were increased and their syntheses by de novo pathways were inhibited in cells treated with RNA synthesis inhibitors. ATP decreased slightly and GTP remained unchanged in growth-arrested cells treated with methotrexate. In growth-arrested cells, de novo purine nucleotide synthesis was inhibited less and RNA synthesis rates were lower than in growing cells. (Author abstract) (45 Refs)

26. INHIBITORS OF GLYCOSYLATION REVERSE RETROVIRAL INTERFERENCE.

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Virology; 119(1):185-192 1982

Cells which are productively infected with retroviruses are extremely resistant to superinfection with the homologous virus. We found that in certain cases, this resistance is largely or entirely eliminated by overnight treatment of the cells with either of two inhibitors of glycosylation (2-deoxyglucose or tunicamycin). This loss of viral interference was accompanied by a loss of gp70 from the cell surface, as demonstrated by surface labeling with 125I and radioimmunoprecipitation. In other cell-virus combinations, these inhibitors gave much smaller reductions in viral interference and in the level of gp70 at the cell surface. The most likely explanation for these phenomena is that inhibition of glycosylation of the env precursor polyprotein prevents its subsequent processing into gp70 and transport to the cell surface; to the extent that the cellular pool of gp70 is depleted during an overnight treatment, cellular receptors become available for interaction with superinfecting virus particles. (Author abstract) (29 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

27. MECHANISM BY WHICH CAFFEINE POTENTIATES LETHALITY OF NITROGEN MUSTARD.

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Proc Natl Acad Sci USA; 79(9):2942-2946 1982

Caffeine is synergistic with many DNA-damaging agents in increasing lethality to mammalian cells. The mechanism is not well understood. Our results show that caffeine potentiates the lethality of the nitrogen mustard 2-chloro-N-(2-chloroethyl)-N-methylethanamine (HN2) by inducing damaged cells to undergo mitosis before properly repairing lesions in their DNA. Treatment with low doses of HN2 (0.5 uM for 1 hr) caused little lethality in baby hamster kidney cells (90% survival). These cells were arrested in G2 shortly after treatment with HN2 as shown by flow microfluorimetry and autoradiography. After an arrest of 6 hr, HN2-treated cells began to move into mitosis and from then on behaved like normal cells. Repair synthesis was shown to continue during the G2 arrest by using synchronized cells pulse labeled with [3H]thymidine after HN2 treatment and autoradiography. Caffeine (2 mM) increased the lethality of HN2 by 5-to 10-fold. It prevented the G2 arrest. Caffeine did not prevent these HN2-treated cells from entering or completing S phase but rather allowed them to divide without finishing the repair processes and as a consequence caused nuclear fragmentation after mitosis. Caffeine-induced nuclear fragmentation and enhanced lethality were proportional, as shown with dose-response curves and time dependence. In addition, both lethality and nuclear fragmentation were abolished by low doses of cycloheximide, an inhibitor of protein synthesis. (Author abstract) (34 Refs)

28. EFFECT OF ASCORBIC ACID ON 5-FLUOROURACIL-6-3H INCORPORATION INTO ACID-SOLUBLE FRACTION AND RNA OF EHRLICH ASCITES CARCINOMA CELLS SENSITIVE AND RESISTANT TO 5-FLUOROURACIL.

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Dept. Biochemistry, Medical Inst., Lvov, USSR
Biull Eksp Biol Med; 93(2):56-57 1982

The effect of ascorbic acid (AA) on the incorporation of labeled 5-fluorouracil (5-FU) was studied in random-bred albino mice with 5-FU-sensitive and 5-FU-resistant Ehrlich ascites carcinoma (EAC). Incubation of tumor cells with AA resulted in marked increase of 5-FU incorporation into the acid-soluble fraction and in the RNA of both sensitive and resistant EAC cells. The rate of 5-FU incorporation into the RNA fraction was approx 10x lower than the rate of incorporation into the acid soluble fraction. These findings indicate that AA can be used in the potentiation of the activity of antineoplastic agents against the resistant tumors. (3 Refs) (In RUS)

29. MECHANISM OF SYNERGISTIC CYTOTOXICITY BETWEEN NUCLEOSIDES AND ARABINOFURANOSYL CYTOSINE (ARA-C) AGAINST HL-60 CELLS (MEETING ABSTRACT)

Akman SA, Ross DD, Joneckis CC, Schrecker AW, Bachur NR
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Proc Am Assoc Cancer Res; 23:865 1982

It is known that Deoxyguanosine (dGuo) and ara-C synergistically inhibit cloning of the human leukemia cell lines HL-60 and K562. We have investigated the mechanism of synergy, comparing the effect of dGuo to that of thymidine (dThd), which increases ara-C triphosphate (ara-CTP) pool size and augments incorporation of ara-C into nucleic acid in other cell lines. We incubated log phase HL-60 cells with 0.1 mM dGuo or 1 mM dThd, concentrations equitoxic for HL-60 cloning, for 24 hrs and analyzed changes in cell cycle and deoxycytidine triphosphate (dCTP) pool size. Both nucleosides increased cellular vulnerability to ara-C and caused partial synchrony in early S phase as shown by flow cytometry. dGuo (0.1 mM) reduced dCTP pool size by 29%, as measured with the Escherichia coli DNA polymerase assay, versus a 61% reduction by dThd (1 mM). In subsequent experiments, we analyzed ara-C metabolism by co-incubating HL-60 cells with 10nM 3H-ara-C, a concentration which does not inhibit cell cloning in absence of deoxynucleosides, and with dGuo or dThd in concentrations from 0.01 to 5.0 mM. dThd increased incorporation of 3H-ara-C into DNA, with a maximal increase of 370% at 1.0mM. As assayed by high pressure liquid chromatography, dThd increased ara-CTP pool size up to a maximum of 145% of control at 0.6 mM. dGuo also increased ara-CTP pool size to a maximum of 193% of control at 0.01 mM, the lowest concentration tested. However, dGuo increased incorporation of ara-CTP pool size to a maximum of 193% of control at 0.01 mM, the lowest concentration tested. However, dGuo increased incorporation of ara-C into DNA only marginally (129% of control) at 0.01 mM, and reduced incorporation at higher concentrations. These data suggest that dGuo and dThd exhibit synergy with ara-C by different mechanisms, since dThd augments its incorporation into DNA, while dGuo does not. (1 Ref)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

30. SOME PROPERTIES OF THE POLYAMINE DEPRIVATION-INDUCIBLE UPTAKE SYSTEM FOR METHYLGLYOXAL BIS(GUANYLHYDRAZONE) IN TUMOR CELLS.

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Acta Chem Scand [B]; 35(10):731-736 1981

Depletion of the intracellular levels of putrescine and spermidine by the ornithine decarboxylase inhibitor, DL-alpha-difluoromethylornithine (DFMO), resulted in an increased uptake of various polyamines and the spermidine analog methylglyoxal bis(guanylhydrazone) (MGBG) by Ehrlich ascites tumor cells. Examination of the kinetics of uptake of MGBG in DFMO-treated cells showed that polyamine deprivation did not influence the affinity of the transport system, since the Km values were about the same for treated and untreated cells. However, the max velocity for uptake was 4x higher for the polyamine-depleted cells. For both treated and untreated cells, the uptake of MGBG was temperature dependent, with similar values of activation energy of uptake. Ouabain, an inhibitor of Na,K-ATPase, decreased the uptake of DFMO in treated and untreated cells with little effect on cellular ATP, suggesting that the uptake is partially Na linked. While iodoacetate greatly decreased the ATP content of treated and untreated cells, it decreased the MGBG uptake much less than did ouabain, indicating that energy production is not an absolute requirement for drug uptake. In the DFMO-treated cells, 3-4x more MGBG was accumulated in the nuclear, mitochondrial, and cytosol fractions, while the level in the microsomal fraction was 7x higher than in untreated cells. These results may explain the potentiation of the antiproliferative action of MGBG by DFMO. (21 Refs)

31. PYRIMIDINE RIBONUCLEOSIDE PHOSPHORYLASE ACTIVITY VS 5-AND/OR 6-SUBSTITUTED URACIL AND URIDINE ANALOGUES, INCLUDING CONFORMATIONAL ASPECTS.

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Biochem Pharmacol; 31(6):1097-1102 1982

The pyrimidine ribonucleoside phosphorylase from Salmonella typhimurium phosphorylyses 6-methyluridine, a uridine analogue sterically constrained to the syn conformation about the glycosylic bond, as effectively as uridine itself. In conjunction with the observation that 3-methyluridine is a very poor substrate compared to 5-methyluridine and 5,6-dimethyluridine, it follows that the phosphorolysis reaction involves the initial conversion of uridine, and other 5-substituted uridines (including 5-fluorouridine), to the syn conformation during interaction with the enzyme. Furthermore, and consistent with the forego-

ing, the enzyme recognizes as substrates, to varying degrees, the N(3)-ribosides of xanthine and uric acid, and will also catalyze the formation of these ribosides from the corresponding purines, which may be considered formally as 5,6-disubstituted uracils. Similar observations are reported for the synthetic 5,6-trimethyleneuridine. The enzyme does not, however, recognize 6-methyluracil and 5,6-tetramethyleneuridine in the reverse, synthetic, reaction. The conformational aspects of these reactions are discussed. Since it was previously shown that 6-methyluridine is an equally effective substrate for the pyrimidine phosphorylase of primary rabbit kidney cells, at least some of these conformational requirements apply to the enzyme from mammalian sources, and are consequently of relevance in the design of chemotherapeutic agents, for which some examples are cited. (Author abstract) (30 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

32. STRUCTURE-ACTIVITY RELATIONSHIPS INVOLVED IN THE SITE-SPECIFIC FRAGMENTATION OF LINEAR DUPLEX DNAS BY TALISOMYCIN AND BLEOMYCIN ANALOGS.

Mirabelli CK, Huang CH, Prestayko AW, Crooke ST
Dept. Pharmacology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030
Cancer Chemother Pharmacol; 8(1):57-65 1982

Site-specificity of DNA breakage by bleomycin (BLM) and talisomycin (TLM) was examined using analogs of the parent compounds and two species of DNA. Fragmentation of Hind III- and PstI-digested PM2 DNA and Hind III-digested pBR322 DNA by BLM A2 and B2 and TLM A, B, S2b, and S10b was compared. With PM2 DNA as a substrate, TLM A was more active than BLM A2 in inducing double strand breakage of whole linear PM2 DNA. Ethidium bromide staining band patterns produced from inactivation of endonuclease-digested DNA with BLM or TLM differed, indicating that certain PM2 genome segments serve as better substrates for double strand fragmentation by BLM or TLM. (31 Refs)

EFFECTS OF ANTIMETASTATIC AGENTS

33. THE ROLE OF MACROPHAGES IN CONTROLLING POST-OPERATIVE METASTASIS OF 3LL (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:1037 1982

It was previously reported that the metastatic spread of the Lewis lung carcinoma (3LL) is low during the growth of a local tumor in the footpad, but greatly enhanced after its removal by amputation of the leg. The aim of the present study was to investigate the role of macrophages in the control of metastasis prior to and following surgery. Mice injected in the footpad with a lethal dose of tumor 3LL received various doses of either carrageenan -- a polysaccharide toxic to macrophages or tuftsin -- a peptide known to stimulate macrophage activity in vivo. The agents were administered ip prior to, simultaneously with, or following the removal of the local tumor. The following observations were made: 1) When injected ip but not into the tumor, carrageenan was effective in enhancing metastasis at every concentration and regimen applied, but more limited in mice whose local tumor was not removed. 2) Mice injected with carrageenan 7 days prior to tumor removal showed the most extensive increase in metastasis, as compared to mice injected simultaneously with or following amputation. 3) The administration of tuftsin was successful in reducing post-amputation metastasis only when injected both prior to and following amputation. These results support the existing body of evidence for the host-protective role macrophages play against metastasis and suggest that in the current tumor model this role is more significant during the growth of the primary tumor. They also indicate the existence of other mechanisms in the control of metastasis during tumor growth. (no Refs)

34. B16 MELANOMA CELL VARIANTS: IRREVERSIBLE INHIBITION OF GROWTH AND INDUCTION OF MORPHOLOGIC DIFFERENTIATION BY ANTHRACYCLINE ANTIBIOTICS.

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JNCI; 68(4):629-638 1982

The interaction of doxorubicin and N-trifluoroacetyladriamycin-14-valerate (AD32) with B16 melanoma cell variants that exhibit distinct metastatic properties was explored. The addition of the two drugs to cell monolayers at noncytolytic concentrations for 16 hr resulted in irreversible inhibition of proliferation of tumor cells and loss of their tumorigenicity after injection into inbred C57BL/6 mice. Cessation of melanoma cell proliferation was accompanied by cellular and nuclear hypertrophy and the development of axon-like processes. As assessed by drug-specific cytofluorescence, after 16-hr exposure of the cells to doxorubicin and AD32, the drugs were localized in the nuclei. Incubation of drug-treated cell monolayers for 6 additional days in drug-free culture medium led to the complete disappearance of nuclear stain. The highly metastatic B16-F10-B2 cell line was the most sensitive to the drugs' effects, whereas the other two malignant melanoma cell lines, although differing in their metastatic capabilities, exhibited similar sensitivities to the drugs' effects. Doxorubicin was notably more potent than AD32 in its growth inhibitory effect on the three tested melanoma cell variants. The possible mutagenic effect of anthracycline drugs on tumor cells was discussed. (Author abstract) (42 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

35. ANTIPROLIFERATIVE ACTION OF A NOVEL FLUORINATED URIDINE ANALOG, 5'-DEOXY-5-FLUOROURIDINE, MEASURED IN VITRO AND IN VIVO ON FOUR DIFFERENT MURINE TUMOR LINES.

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Pharmaceutical Res. Dept., F. Hoffmann-LaRoche and Co., Ltd., CH-4002 Basel, Switzerland
Cancer Res; 42(6):2412-2415 1982

The antiproliferative action of a novel fluorinated uridine analog, 5'-deoxy-5-fluorouridine (5'-dFUrd; Ro 21-9738), and its predecessors, 5-fluorouracil (FUra) and 2'-deoxy-5-fluorouridine (FdUrd), was measured in vitro during the logarithmic growth phase on four different murine tumor cell lines (3 LL, S 180, YAC 1, and B 16). 5'-dFUdr was growth inhibitory for 3 LL, S 180, and YAC 1 but proved to be ineffective against B 16. The concentrations of 5'-dFUrd needed to diminish growth of the sensitive lines by 50% were 10 to 50x higher than those needed for FUra. Still larger differences existed between 5'-dFUrd and FdUrd, the latter proving to be the most potent drug in vitro and highly effective against B 16. The growth-inhibitory action of FdUrd could be antagonized by thymidine but not by uridine (with the notable exception of the YAC 1 cell line); 5'-dFUrd, however, could be antagonized both by thymidine and uridine. In vivo, when tested against the same cell lines as those used in vitro, 5'-dFUrd proved to have an effect similar to that of FdUrd. In addition, 5'-dFUrd was much less toxic for the tumor-bearing hosts. In order to explain the discrepancy between in vitro and in vivo results, the hypothesis put forward recently that a differential conversion of 5'-dFUrd to the toxic FUra metabolite might explain both the relative insensitivity of tumor cell lines towards 5'-dFUrd in vitro and the low toxicity in vivo was tested. The rate of conversion of FdUrd and 5'-dFUrd to FUra was measured in normal mouse liver (of the same strains as the tumor-bearing hosts) and in the four tumor cell lines. The relatively high activity of pyrimidine nucleoside phosphorylase, an enzyme which is more able to convert 5'-dFUrd into FUra in tumor tissue than in normal tissue, might at least partially explain the discrepancies between in vitro and in vivo results although the correlations were by no means quantitative. (Author abstract) (16 Refs)

36. AGENTS WITH POTENTIAL SPECIFICITY AGAINST MELANOTIC MELANOMA.

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Lab. Medicinal Chemistry and Biology, NCI, NIH, Bethesda, MD, 20205
J Med Chem; 25(5):501-505 1982

Agents were designed to exploit the high tyrosinase activity in melanotic melanoma relative to normal tissues. If specific tyrosinase activation of these agents occurred, the production of toxic metabolites in the melanoma cells would produce selective cell kill. Synthesis and antitumor activities of three new amino acids, (1a) [beta-[(p-hydroxyphenyl)amino]alanine hydrochloride], (1b) [Ndelta -(p-hydroxyphenyl)ornithine hydrochloride], and (1c) [Ndelta-(m-hydroxyphenyl)ornithine dihydrochloride], were described. Compounds 1a and 1b were approx two-fold more active against the B-16 melanotic melanoma than the amelanotic melanoma cell line in vitro. Compound 1b was approx two-fold more potent than compound 1a against either cell line and was eight-fold more potent than L-glutamic acid gamma-(4-hydroxyanilide), a natural product isolated from mushroom. No significant growth inhibitory activity was found for the m-hydroxy analogue 1c at 100 uM, the highest concentration tested. Similarly, compound 1b exhibited better activity against P-388 (ED50 = 9.5 x 10(-6) M) than 1a (ED50 = 3.2 x 10(-5) M) and was about 30-fold more potent than 1c. Against human epidermoid carcinoma of the nasopharynx (KB), these agents showed modest inhibitory activity with ED50 values in the range of 1.2 to 3 x 10(-4) M. No in vivo activity against P-388 and B-16 at doses up to 150-200 mg/kg was observed. The biological results suggest that a nonspecific oxidation rather than a specific tyrosinase activation is involved in the biological action of these new compounds. (Author abstract) (21 Refs)

37. POLYHYDROXYBENZOIC ACID DERIVATIVES AS RIBONUCLEOTIDE REDUCTASE INHIBITORS AND ANTITUMOR AGENTS (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:798 1982

Our group has been involved in the development of a new series of anticancer agents that appear to work by inhibition of ribonucleotide reductase (RR). The basic active structure contains a vicinal polyhydroxy or polyamino aromatic ring. The initial members of this series exhibiting good antitumor activity have, in addition to the basic polyhydroxyphenyl ring, a hydroxamic acid side chain, a structural moiety known to inhibit RR. The hydroxamic acid is not essential, since amides, esters and other groups have good enzyme inhibition and antitumor activity. On the other hand, in contrast to the hydroxamic acids, non adjacent polyhydroxbenzoic ester and amides are not effective enzyme inhibitors or antitumor compounds. The relative importance of the position and kind of substitution on the ring for enzyme inhibition is demonstrated with a series or ring substituted benzamides to eliminate the inhibitory contribution of the hydroxamic acid group. Only the vicinal hydroxy groups demonstrated any appreciable activity. Replacement of one of the two hydroxyl groups with a methoxy group resulted in a loss of activity. Since the 3,4-dihydroxy and 3,4,5-trihydroxy phenyl structures are present in the most effective agents of this series, the antitumor activity reported for DOPA analogs and other catechol compounds also appears to be partly the result of RR inhibition. The relative potency of a series of DOPA analogs on RR, parallels their antileukemic activity and demonstrates the structural constraints of the side chain. The mechanism of action of the polyhydroxy compounds appears to be related to their ability to scavenge free radicals. (no Refs)

38. DL-THREO-BETA-FLUOROASPARTATE AND DL-THREO-BETA-FLUOROASPARAGINE: SELECTIVE CYTOTOXIC AGENTS FOR MAMMALIAN CELLS IN CULTURE.

Stern AM, Foxman BM, Tashjian AH, Abeles RH
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J Med Chem; 25(5):544-550 1982

Absolute configuration assignments have been made for the diastereomers of DL-beta-fluoroaspartate by x-ray analysis. The cytotoxicity of these isomers against various mammalian cells was examined. DL-threo-beta-fluoroaspartate shows selective cytotoxicity. Growth of the most sensitive cells is completely inhibited by 13 uM DL-threo-beta-fluoroaspartate in the presence of 100 uM L-aspartate, a component of the culture medium. A difference in the rate of transport of DL-beta-fluoroaspartate among the cells studied is an important factor determining cell specificity. For those cell that are sensitive to DL-beta-fluoroaspartate, the threo isomer is, in all cases, more potent than the erythro isomer. Radioactivity derived from L-threo-beta-fluoro[14C]aspartate is incorporated into proteins at a rate comparable to the rate of incorporation from L-[14C]aspartate. We synthesized DL-threo-beta-fluoroasparagine. This compound is also cytotoxic but less specific and less potent than DL-threo-beta-fluoroaspartate. However, the cell specificity can be enhanced in the presence of 1 mM L-aspartate, which can protect some cells but not others from the cytotoxic effects of DL-threo-beta-fluoroasparagine. Jensen sarcoma cells, which require asparagine, are not protected by L-aspartate. Therefore, a combination of L-aspartate and DL-threo-beta-fluoroasparagine can be used to inhibit specifically the growth of asparagine-requiring tumors. (Author abstract) (45 Refs)

39. SYNTHESIS AND ANTITUMOR ACTIVITY OF ETHYL ETHER OF 4-(DI-(2,-CHLOROETHYL)AMINO)-L-PROLINE.

Koksharova TG, Rozin IuA, Sokolova VN, Barybin AS, Zubova TE, Pushkareva ZV, Lobova TG, Sof'ina ZP
S. M. Kirov Polytechnical Inst., Sverdlovsk, USSR
Khim Farm Zh; 16(3):284-287 1982

Antitumor activity of newly synthesized ethyl ether of 4-(di-(2,-chloroethyl)amino)-L-proline (compound Ia) was studied in BDF mice bearing leukemia L1210, leukemia P388, leukemia L5178Y, and melanoma B-16, in C57BL mice bearing leukemia La, adenocarcinoma Ca-755, and Lewis lung carcinoma, and in random-bred rats bearing Walker 256 carcinosarcoma. Compound Ia provided mild inhibition of leukemias L1210 and P388, marked inhibition of leukemia L5178Y, and 70-100% inhibition of Ca-755. Compound Ia was ineffective against leukemia La, Lewis lung carcinoma, and melanoma B-16. Compound Ia penetrated the brain-blood barrier and inhibited the growth of intracerebrally transplanted Walker carcinosarcoma. (3 Refs) (In RUS)

INTERFERON AND OTHER ANTIVIRALS

40. SEQUENTIAL IN VITRO ACTIVATION OF HUMAN PBL BY SEPARATE CLONED HUMAN INTERFERONS (IFN) ENHANCES NK CELL CYTOTOXICITY (NK CC) GREATER THAN SIMULTANEOUS OR SINGE AGENT TREATMENT ALONE (MEETING ABSTRACT)

Targan S, Stebbing N
Wadsworth Veterans Administration Medical Center, University of, California Los Angeles, CA
Fed Proc; 41(3):957 1982

Previously, we have shown that sequential activation of NK cells by different modulators (ie IFN and Prostaglandin E2) enhanced cytotoxic activity against K562 or Molt-4 better than each alone. We have extended these observations using three purified cloned human interferons. The human leukocyte interferon subtypes IFN-alpha A, IFN-alpha D and cloned human fibroblast IFN, IFN-beta 1 were tested alone and in combination either with simultaneous or sequential treatment of normal human PBL for their capacity to enhance NKCC against K562 or Molt-4 target cells. At comparable concentrations, IFN-beta 1 enhanced NK (natural killer) activity greater than IFN-alpha A or IFN-alpha D. Simultaneous administration of IFN-alphaA and -alpha D, IFN-beta 1 and -alpha A or IFN-beta 1 and -alpha D did not enhance NKCC above each agent alone. However, sequential 1 hour activations of PBL first by one IFN and then a different IFN either IFN-beta 1 or a different IFN-alpha subtype further activated NK cells. The data indicate that combinations of different cloned human IFN's using a sequential activation protocol which alternates IFN types could be much more effective than single agent administration in enhancing in vivo NK activity. This might be useful in treatment of neoplasia or viral infection where NKCC may be an important host defense factor. (no Refs)

41. CHANGES IN DNA-POLYMERASE AND THYMIDINE KINASE ACTIVITY DURING INTERFERON TREATMENT.

Lundblad D, Lundgren E
(c/o Lundgren) Lab. for Cell and Tissue Culture Res., Umea Univ., S-901 87 Umea, Sweden
Biochem Biophys Res Commun; 105(4):1569-1576 1982

The effect of human interferon beta (IFN-beta) on the human glioma cell line, U-251 MG, was investigated. Exponentially growing cells treated with IFN exhibited a dose-dependent growth depression observed after 3 days, and an increase in the amount of cells in S phase. However, the activity of DNA polymerase was decreased to 30% of control levels at day 5 with 1,000 Units/ml of IFN-beta. This depression in enzyme activity may be explained by an inhibitory effect of IFN on the increase of enzyme activities induced by events in late G1 or early S, or by the induction of diffusable factors depressing enzyme activities. Starved cells were induced to cycle and DNA content was followed cytofluorometrically. S phase started approx 12 hr after addition of serum to synchronized cells and cells entered G2 at 21 hr. In contrast, IFN-treated cultures initiated S but accumulated in that phase. At the start of S phase, both DNA polymerase and thymidine kinase activity increased, although the rate of increase was markedly reduced by treatment with IFN. No inhibitory factor could be identified in the IFN treated cultures. It is probable that IFN has a direct effect on the induction of the studied enzyme activities, thus affecting virus replication. (18 Refs)

42. ANTIVIRAL EFFECTS OF INTERFERON ON A SOMATIC CELL HYBRID BETWEEN TWO BURKITT'S LYMPHOMA CELL LINES OF DIFFERENT INTERFERON SENSITIVITIES.

Lidin B, Lamon EW
(c/o Lamon) Dept. Microbiology, Cancer Res. and Training Center, Birmingham Veterans Admin. Hosp., Univ. Alabama in Birmingham, Birmingham, AL, 35294
Infect Immun; 36(2):847-849 1982

A somatic cell hybrid between two human Burkitt's lymphoma cell lines, Raji and Daudi, was infected with either Epstein-Barr virus or vesicular stomatitis virus after interferon treatment. Raji cells are resistant to the antiviral effects of exogenously added interferon, whereas Daudi cells are interferon sensitive. The Raji-Daudi hybrid showed an interferon sensitivity that was intermediary to that of the parental cells against both viruses. (Author abstract) (14 Refs)

43. MOLONEY MURINE SARCOMA VIRUS TUMORS IN CBA/J MICE: CHEMOPREVENTIVE AND CHEMOTHERAPEUTIC ACTIONS OF SUPPLEMENTAL BETA-CAROTENE.

Seifter E, Rettura G, Padawer J, Levenson SM
Dept. Biochemistry, Albert Einstein Coll. Medicine, Yeshiva Univ., Bronx, NY, 10461
JNCI; 68(5):835-840 1982

Decreased tumor frequency, increased latent period, and increased rate of tumor regression were observed in male inbred CBA/J mice fed supplemental beta-carotene before and/or after they were inoculated with the Moloney sarcoma virus. When beta-carotene feeding was begun after tumors were already present, it markedly increased the rate of tumor regression. Beta-carotene minimized the virus-induced thymus gland involution that accompanies tumor growth, and this action on the thymus gland was believed to underlie part of beta-carotene's antitumor activity. The basal diet, a standard commercial mouse chow containing more vitamin A than the National Research Council recommends as a daily allowance for rodents, supported normal growth, reproduction, and longevity of normal mice. The work reported here is the first demonstration of the antitumor action of carotene in mice inoculated with an oncogenic virus. (Author abstract) (34 Refs)

44. ANTIVIRAL EFFECTS OF DEOXYPODOPHYLLOTOXIN ON HSV-INFECTED AMNION CELL CULTURES.

Markkanen T, Makinen ML, Miettinen J, Laijoki T, Maunuksela E, Hietanen T, Lehto I, Himanen P
Clinical Res. Lab., Univ. Turka, SF-20520 Turka 52, Finland
Drug Exp Clin Res; 8(1):27-34 1982

The effect of deoxypodophyllotoxin (DPT) on normal and herpes simplex-1 virus (HSV)-infected human amnion cell cultures was investigated. DPT sharply decreased the incorporation of thymidine, and moderately increased the incorporation of uridine and methionine in both normal and infected cells. The DPT-treated infected cultures showed no viral cytopathogenic effect. When DPT was removed by washing, incorporation of thymidine increased back to normal levels. DPT inhibited the proliferation of HSV, and did not exhibit virucidal activity. (14 Refs)

45. A COMPARISON OF THE REQUIREMENTS FOR ANTITUMOR ACTIVITY AND ANTIBACTERIOPHAGE LAMBDA ACTIVITY FOR A SERIES OF NON-INTERCALATIVE DNA-BINDING AGENTS.

Robertson IG, Baguley BC
Lab. Molecular Genetics, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Eur J Cancer Clin Oncol; 18(3):271-279 1982

A series of non-intercalative DNA-binding agents, comprising mainly bisquaternary ammonium heterocyclic compounds, has been found to inhibit strongly the production of bacteriophage lambda following its induction in Escherichia coli. The inhibition is much greater than that found with a number of DNA intercalating agents, including 9-aminoacridine, ethidium and Daunorubicin. The inhibition correlated significantly with antitumor effect, as measured in a life extension assay with L1210 leukemia. Activity in both biological systems demanded the presence of strongly charged groups and a rigid co-planar aromatic skeleton, these requirements being almost identical to those needed to displace ethidium efficiently from DNA in a simple assay system. It is suggested that biological activity is associated with the ability of these agents to bind in the minor groove of the DNA double helix. Data on the antibacteriophage action of one of these agents suggests possible models for antitumor activity. (Author abstract) (18 Refs)

46. DIFFERENTIAL INHIBITION OF DNA POLYMERASE AND RNASE H ACTIVITIES OF THE REVERSE TRANSCRIPTASE BY PHOSPHONOFORMATE.

Margalith M, Falk H, Panet A
Dept. Virology, Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel
Mol Cell Biochem; 43(2):97-103 1982

Three potential inhibitors of reverse transcriptase activities, phosphonoformate (PF), phosphonoacetate (PAA), and ethyldiethyl phosphonoformate (Et-PF), were compared in this study. Only PF was found to inhibit the DNA polymerase activity of the purified reverse transcriptase of Moloney murine leukemia virus (M-MuLV) and avian myeloblastosis virus (AMV). The degree of DNA polymerase inhibition was linear with PF concentration; 50% inhibition was achieved at 10 uM. Whereas PF inhibited both the RNA and DNA dependent DNA polymerase activities, the RNase H activity of the reverse transcriptase was unaffected. Both the endogenous DNA polymerase activity in detergent disrupted virus and the activity of the purified enzyme with the isolated virus genome 70S RNA were inhibited by PF. However, higher concentrations of PF were needed to inhibit the endogenous reaction. The inhibition by PF appeared to be reversible and noncompetitive with respect to the substrate deoxythymidine triphosphate (dTTP). Addition of PF after the initiation of DNA synthesis immediately arrested the reaction. (Author abstract) (26 Refs)

47. MECHANISM OF RESISTANCE TO ARA-C IN A MUTANT HERPESVIRUS (MEETING ABSTRACT)

Schnipper LE, Crumpacker CS, Antman K, Kufe D
Harvard Medical School, Boston, MA, 02215
Proc Am Assoc Cancer Res; 23:868 1982

Ara-A (adenine arabinoside) (ara-A) and cytosine arabinoside (ara-C) are effective inhibitors of cellular and Herpes Simplex virus type 1 (HSV-1) DNA synthesis. A mutant of HSV-1 (Ara-Ar) selected in ara-A, and resistant to both ara-A and ara-C has been employed to study mechanisms of resistance to arabinofuranosyl derivatives. Incorporation of ara-C into wild type HSV-1 (KOS) and HSV-1 (ara-Ar) DNA was monitored by isopycnic centrifugation of viral DNA with 3H-ara-C and 32P 6-20 hours post-infection of Vero cells. 32P labelling serves as a measure of relative rates of DNA synthesis. At a concentration of 5 x 10-7M ara-C, the ratio of 3H-ara-C to 32P incorporation into DNA was 0.1 for HSV-1 (ara-Ar) compared to 1.0 for HSV-1 (KOS). When compared to KOS, DNA synthesis with Ara-Ar was less inhibited by ara-C up to a concentration of 5 x 10-6M and was associated with formation of less ara-C DNA. Above 5 x 10-6M there is linear incorporation of 3H-ara-C into mutant viral DNA, and inhibition of DNA synthesis comparable to that in HSV-1 (KOS). High pressure liquid chromatographic analysis of purified viral DNA digested to 3'-nucleotides demonstrates that ara-C is incorporated into internucleotide linkage in both wild type and mutant viruses, between 10(-7)-10-5M. At high concentrations (greater than 10-5M), a greater proportion of ara-C residues are present at the chain terminus. The extent of ara-C incorporation into DNA correlates with inhibition of plaque formation such that HSV-1 (ara-Ar) is insensitive to concentrations less than 5 x 10-6M, whereas HSV-1 (KOS) plaque formation is inhibited in linear fashion between 10(-7)-10-4M. HSV-1 (ara-Ar) resistance to ara-C is overcome above concentrations of 5 x 10-6M. Resistance to ara-C is closely related to exclusion of this analog from viral DNA, however, the precise enzymatic mechanism is not yet understood. (no Refs)

48. DIETHYLDITHIOCARBAMATE (DDC)-MEDIATED BLOCKADE OF NATURAL KILLER (NK) CELL ACTIVITY: RELATIONSHIP TO INTERFERON (IFN) EFFECTS (MEETING ABSTRACT)

Edwards BS, Fox RW, Merritt JA, Borden EC
University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:1062 1982

The ability of IFNs to augment NK cell activity and the ability of anti-IFN antisera to block, not only augmentation, but also the basal expression of NK cell activity, suggest that IFNs serve a fundamental role in NK cell regulation. DDC blocks IFN-mediated development of the antiviral state, possibly by its inhibitory effects upon superoxide dismutase. Therefore, to further examine the role of IFNs in NK cell function, we treated human peripheral mononuclear cells with DDC and assessed NK cell reactivity to K562 target cells in 6-hr Cr-51 release assays. At concentrations of 10(-6) to 10(-4), DDC inhibited basal NK cell activity 50-95% without affecting cell viability. In 2 of 3 experiments, DDC-inhibited NK cells spontaneously recovered function within 24-48 hr of treatment. One hr treatment with IFN, sufficient to enhance NK cell activity of controls 2-3 fold, failed to boost activity of DDC-treated NK cells. However, continuous incubation of DDC-pretreated cells with IFN for 24 hr resulted in levels of NK cytotoxicity equal to or greater (depending upon DDC pretreatment dose) than in control cells exposed only to IFN. We conclude that a DDC-sensitive enzyme(s) is required for IFN-mediated stimulation of NK cells. Reduction of basal NK cell activity by DDC is furthermore consistent with a role for IFN in NK cell functional maintenance. (no Refs)

49. ROLE OF DNA INCORPORATION IN THE MECHANISM OF ACTION OF 6-THIOGUANINE (6-TG) (MEETING ABSTRACT)

Drake S, Carpenter P, Nelson JA
Department of Experimental Pediatrics, M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Fed Proc; 41(3):1566 1982

An antitumor agent, (6-TG) may alter cell viability and/or function due to incorporation into DNA. For example, the transforming activity of Bacillus subtilis DNA is reduced in a dose-dependent manner proportional to the incorporation of 6-TG. To test if other biological functions of DNA are altered by the base analog, a DNA virus (vaccinia) was grown in HeLa cells treated with 6-TG. The virus was extracted from the cells by sonication and purified by centrifugation on 25-60% sucrose density gradients. The buoyant density of the virus grown in the presence of 6-TG was more heterogeneous than control virus. However, no apparent physical abnormalities were discernible by electron microscopy, and the virions were not sensitive to deoxyribonuclease. Total infectious virus production was reduced 100-fold by treatment with 6-TG (30 ug/ml for 24 hrs) during infection; however, there was only a 6-fold reduction in particle formation. The ability of such particles to induce DNA synthesis in newly infected cells was also reduced markedly. These effects of 6-TG on vaccinia virus infectivity and viral genome expression may be a consequence of incorporation of the drug into the viral DNA. (no Refs)

OTHER RELATED STUDIES

50. A NEW SUGGESTION FOR THE DESIGN OF RATIONAL ANTICANCER THERAPY: EXPERIMENTAL STUDIES IN MICE.

Setala K
Uimarinpolku 10 B 10, SF-00330 Helsinki 33, Finland
Med Hypotheses; 8(3):207-230 1982

The specific target and mode of action of dimethylsulfoxide (DMSO)-complex was investigated utilizing colchicine (CH) and vinblastine sulfate (VS) as model systems. Approx 30,000 mice with varying degrees of inherited susceptibility towards skin tumor formation were used. Parallel studies comprised tumor-production series, light, polarization, and electron microscopy, histochemical and histoquantitative examination, and in vitro analyses on various mixed lipoprotein surface films. The typical effects of CH and VS on normal epidermis (NE) were a high incidence of drug-dependent 'monster cells' (MC), great increase in cytoplasmic vol, strong intracellular vacuolization, and unmasking of a pre-existent or partly newly developed, coarse, partly ruptured, fibrous cytoskeleton. The mode and strength of response of benign epidermal condition (BEC) were in principle similar to those of NE. The alterations in malignant epidermal condition (MEC) caused by CH and VS were a very weak mode of response, sparsness of MC, low degree of intracellular vacuolization, and only slight additional alterations within the cytoskeleton. The alterations developing in NE after exposure to CH, VS and DMSO were distinctly sparser than without DMSO and the pathological mitoses showed a shift towards the c-type mitoses. The alterations provoked in BEC closely resembled those developing in NE. Recovery from the injury was evident at 72 hr. Exposure of MEC to DMSO, CH, and VS changed the originally cytostatic-insensitive malignant cells to highly susceptible. The reaction was extremely vigorous while the cells were injured to such an extent that cytokinesis was not any more possible and the cells were doomed to die, and the response was characterized by morphogenic patterns indicating a high degree of rehydration through over-imbibition with water of the malignant cells. (65 Refs)

51. EXPERIMENTAL METHODS IN CANCER THERAPEUTICS.

Widder KJ, Senyei AE, Sears B
Kendrew Biosystems, Incorporated, San Diego, CA
J Pharm Sci; 71(4):379-387 1982

Two major approaches for achieving the maximal toxicity of the drug for the tumor while the systemic toxicity is minimized are discussed. The first consists of new types of liposomes which impart an element of selectivity to desired target sites; the second consists of magnetically responsive drug-carrying microspheres which are capable of being targeted to tissue sites by use of an external magnetic field. Physiological fate of liposomes, incorporation of glycolipids and immunoglobulins, use of biological factors and transition temperature, and preparation and in vivo testing of magnetically responsive albumin microspheres are discussed. (59 Refs)

52. CHANGES IN LACTIC ACID CONTENTS IN METASTATIC LIVER TUMORS AND NORMAL LIVER TISSUES IN RAT FOLLOWING GLUCOSE ADMINISTRATION INTO HEPATIC ARTERY.

Iwamoto Y, Nishikawa K

Cancer Res. Inst., Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan

Fukuoka Igaku Zasshi; 73(2):84-89 1982

Active glycolytic action is a characteristic of the cancer cells. Consequently, due to accumulation of lactic acid as a consequence of glycolysis, the pH in the cancer cells is lower than in the normal cells. Using metastatic liver tumor-carrying mice, glucose was fed through hepatic artery, portal vein, or femoral vein, and then the amount of lactic acid in cancer cells and in normal cells was measured. When hepatic artery was the route, the amount of lactic acid increased significantly, and the difference from the normal cells was the greatest compared to those using other routes. The result suggests that a superior anti-liver tumor activity may be obtained by giving an anti-tumor agent that increases the anti-tumor activity at a low pH after injecting glucose through the hepatic artery. (8 Refs) (In JPN)

53. ALTERED TISSUE REACTIVITY AND INTERACTIONS BETWEEN CHEMICALS.

Witschi HP

Oak Ridge Natl. Lab., Oak Ridge, TN

Proceedings of the NRC Workshop on Multichemical Contamination, held in Milan, Italy, April 1981. Available from National Technical Information Service, Springfield, VA, as DE81023189:, 33 pp., 1981.

Interactions between chemicals may modify the biological response if exposure is simultaneous or sequential. Two different situations can be distinguished where interactions are caused by sequential exposure: (1) a first agent acts as an inducer or inhibitor of mixed function oxidases. This alters the response to a second, challenging agent. The nature of the biological response, whether enhanced or abolished, is dictated by the second agent; and (2) a first agent produces slight or possibly undetected or undetectable changes in a tissue. Exposure to a second agent enhances or allows expression of the biological response determined by the first agent. Both types of interactions are characterized by a requirement for a strictly ordered sequence of exposure to two chemicals and by complex dose-effect and time-effect relationships. Detection of such interactions is not likely to occur if exposure is simultaneous or unless specific experimental questions dealing with the nature and modification of the biological response are explored. (Author abstract)

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EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. CYTOTOXICITY AND DNA STRAND BREAKS BY 5-IMINODAUNORUBICIN IN MOUSE LEUKEMIA L1210 CELLS: COMPARISON WITH ADRIAMYCIN AND 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE.

Zwelling LA, Kerrigan D, Michaels S
NCI, Building 37, Room 5D17, 9000 Rockville Pike, Bethesda, MD, 20205
Cancer Res; 42(7):2687-2691 1982

The effects upon cellular DNA and cytotoxicity produced by the anthracyclines 5-iminodaunorubicin and adriamycin were studied in mouse leukemia L1210 cells. 5-Iminodaunorubicin produced protein-concealed DNA strand breaks as measured by alkaline elution as had other intercalators including adriamycin. 5-Iminodaunorubicin produced DNA breaks more more efficiently than did adriamycin despite a lower potency for free radical formation. Many of the 5-iminodaunorubicin breaks measured in this assay may arise from apposed single-strand breaks (ie, double-strand breaks). 5-Iminodaunorubicin

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produced breaks which disappeared within 1 and 2 hr following drug removal and were in this way similar to the breaks produced by the acridine intercalator 4'-(9-acridinylamino)methanesulfon-m-anisidide. Adriamycin produced more persistent breaks. Despite similarities in the kinetics of break disappearance, 5-iminodaunorubicin produced greater cytotoxicity than did 4'-(9-acridinylamino)methanesulfon-m-anisidide when compared at doses producing equal single-strand or double-strand breaks. Differences in the ratio of single-strand breaks to double-strand breaks and the associated cytotoxicity for 4-iminodaunorubicin and 4'-(9-acridinylamino)methanesulfon-m-anisidide indicate that a different mechanism is probably involved in the DNA break production by each agent. Differences between the cytotoxicity associated with the DNA break production by two agents with similar break disappearance kinetics indicate that intercalator-induced DNA breaks cannot be a uniformly lethal DNA lesion. (Author abstract) (22 Refs)

2. ETHIDIUM BROMIDE CHANGES THE NUCLEASE-SENSITIVE DNA BINDING SITES OF THE ANTITUMOR DRUG CIS-DIAMMINEDICHLOROPLATINUM(II).

Tullius TD, Lippard SJ
(c/o Lippard) Dept. Chemistry, Columbia Univ., New York, NY, 10027
Proc Natl Acad Sci USA; 79(11):3489-3492 1982

Exonuclease III has been shown previously to reveal the binding sites of the antitumor drug cis-diamminedichloroplatinum(II) on DNA. Pretreatment of the same DNA with the intercalator ethidium bromide causes new platinum binding sites to be detected by the exonuclease III method. In particular, a 5' d(G6-C-G2)3' sequence in a 165-base-pair restriction fragment of plasmid pBR322 becomes a preferred site for exonuclease III-detectable cis-diamminedichloroplatinum(II) binding. This switching of nuclease-sensitive platinum binding to new sites by the influence of another drug, ethidium bromide, offers an explanation at the molecular level for the phenomenon of synergism in combination chemotherapy. (Author abstract) (19 Refs)

3. MECHANISM OF ACTION OF THE ANTITUMOR ANTIBIOTIC CC-1065 (MEETING ABSTRACT)

Rokem JS, Hurley LH
Drug Dynamics Institute, College of Pharmacy, University of Texas, Austin, TX
129th APLA Annual Meeting, April 24-29, 1982, Las Vegas, Nevada. American Pharmaceutical Association and Academy of Pharmaceutical Sciences 101 pp., 1982.

The reaction of CC-1065 with DNA has been investigated using SI-nuclease, and competition binding with anthramycin. CC-1065 is a remarkably potent antitumor antibiotic that inhibits nucleic acid biosynthesis in procaroytic and eucayotic systems. Previous studies published by the Upjohn group have shown that the drug appears to bind to DNA in a covalent nature and has a specificity for A-T base pairs. Using SI-nuclease digestions we have demonstrated that CC-1065 does not appear to distort the DNA structure, but causes stabilization of the helix. Experiments using anthramycin as a probe have shown that both CC-1065 and anthramycin bind in the minor groove, but at low binding rates there is an absolute difference in sequence specificity between the two agents. Based upon these studies a CPK model of the CC-1065-DNA adduct is proposed in which the drug is bound covalently in the minor groove of DNA. (no Refs)

4. MORPHOLOGICAL TRANSFORMATION, DNA STRAND SEPARATION, AND ANTINUCLEOSIDE IMMUNOREACTIVITY FOLLOWING EXPOSURE OF CELLS TO INTERCALATING DRUGS.

Neubort S, Liebeskind D, Mendez F, Elequin F, Hsu KC, Bases R
(c/o Bases) Radiobiology Section, Dept. Radiology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Mol Pharmacol; 21(3):739-743 1982

Two structurally similar alkylating agents, the acridine derivatives proflavine and quinacrine were compared for their ability to induce morphological transformation and DNA strand separation in mouse 3T3 cells. The technique of antinucleoside immunofluorescence staining was used to detect the unwinding of DNA in nuclei of fixed cells. Treatment with proflavine resulted in higher transformation frequencies than were found with quinacrine. Results suggest that DNA strand separation is, or at least accompanies, an early step in cell transformation by intercalating drugs. (28 Refs)

5. THE CONFORMATION AND ORIENTATION OF COPPER(II)-BLEOMYCIN INTERCALATED WITH DNA.

Shields H, McGlumphy C, Hamrick PJ
Dept. Physics, Wake Forest Univ., Winston-Salem, NC, 27109
Biochim Biophys Acta; 697(1):113-120 1982

EPR data are used to describe the conformation and identity of the atoms coordinated to Cu(II) in Cu(II)-bleomycin bound to oriented DNA fibers. The fibers were slowly drawn from viscous solutions of Cu(II)-bleomycin-DNA containing one Cu(II)-bleomycin to 200 basepairs. EPR measurements were made at room temperature and 90 K for different orientations of the external magnetic field with respect to the helical axes of the fibers. The g-values and the hyperfine constant are consistent with values expected for Cu(II) chelated to a square planar array of ligands. In the oriented fibers, the square planar arrays do not all have the same orientations with respect to the fiber axes. At room temperature the chelated ions have rotational freedom in which the normal to the planar array has almost complete freedom of rotation about axes perpendicular to the DNA fiber axes. The normal maintains an angle of 75 degrees with respect to the axis, in the plane of the basepair, about which it rotates. Nine superhyperfine peaks on the high field side of the EPR spectrum were partially resolved. The number and splitting (12 G) of these superhyperfine peaks indicate that four nitrogen atoms are chelated to Cu(II) in a square planar array. These data on Cu(II)-bleomycin bound to DNA give information on the orientation of the metal-containing portion of bleomycin which lies outside the double helix. (Author abstract) (23 Refs)

6. BLEOMYCIN AND TALISOMYCIN SEQUENCE-SPECIFIC STRAND SCISSION OF DNA: A MECHANISM OF DOUBLE-STRAND CLEAVAGE.

Mirabelli CK, Ting A, Huang CH, Mong S, Crooke ST
Smith Kline and French Lab., P.O. Box 7929, Philadelphia, PA, 19101
Cancer Res; 42(7):2779-2785 1982

Computer analyses of DNA sequencing data obtained using various restriction fragments of pBR 322 DNA indicate that a trinucleotide sequence (-Pyr-G-C-) is the most preferred site for cleavage by the antitumor antibiotic bleomycin A2. Talisomycin A, a structurally related bleomycin analog, cleaved at the sequences-G-T/A- most preferentially. However, the presence of a pyrimidine at the 5' side of guanine at the cleavage site did not increase the probability of that site being cleaved by talisomycin. Using denaturing and nondenaturing polyacrylamide gel analyses of the drug-DNA reaction products, the sites of both single- and double-strand breaks have been localized and differentiated. The results indicate that a major determinant for location of a site-specific double-strand break is the production of two closely spaced sequence-specific single-strand breaks by the drugs on opposite strands of the DNA. A four-base pair sequence is proposed for the optimal sequence for bleomycin-induced double-strand breaks. (Author abstract) (26 Refs)

7. REACTION OF ANTHRAMYCIN WITH DNA. BIOLOGICAL CONSEQUENCES OF DNA DAMAGE IN NORMAL AND XERODERMA PIGMENTOSUM CELL LINES.

Petrusek RL, Uhlenhopp EL, Duteau N, Hurley LH
(c/o Hurley) Drug Dynamics Inst., Coll. Pharmacy, Univ. Texas at Austin, Austin, TX, 78712
J Biol Chem; 257(11):6207-6216 1982

Anthramycin, an antitumor antibiotic produced by Streptomyces refuineus, produces a well defined covalent adduct with DNA and lies within the narrow groove of DNA, attached through a thermal-labile covalent animal linkage to the exocyclic amino group of guanine, without detectable distortion of the helix. This paper described results in which the biological consequences of DNA damage and repair by repair-proficient and a repair-deficient xeroderma pigmentosum (XP 12RO) cell line are presented. Anthramycin has been shown to produce excision-dependent single and double strand breaks in DNA, both of which appear to persist many hours after removal of the drug from the media. The lower ability of the xeroderma pigmentosum cell line to remove anthramycin lesions from DNA is correlated with a decreased cell survival. The biological consequences of DNA damage (genetic effects, DNA strand breakage, and cytotoxicity) are discussed with respect to the defined structure and stability of the anthramycin-deoxyguanosine adduct. (Author abstract) (31 Refs)

8. INCREASED RELATIVE EFFECTIVENESS OF DOXORUBICIN AGAINST SLOWLY PROLIFERATING SARCOMA 180 CELLS AFTER PROLONGED DRUG EXPOSURE.

Ritch PS, Occhipinti SJ, Skramstad KS, Shackney SE
Hematology-Oncology Section, Dept. Medicine, Medical Coll. Wisconsin, 8700 W. Wisconsin Ave., Milwaukee, WI, 53226
Cancer Treat Rep; 66(5):1159-1168 1982

Doxorubicin (ADR) lethality was studied in Sarcoma 180 cells grown in vitro during log phase and early plateau phase. For both log phase and plateau phase cells, ADR lethality increased progressively with continuous drug exposure, and was dependent on drug concentration at every point in time. For any given level of toxicity to log phase cells, greater killing of plateau phase cells was achieved with prolonged drug exposure. The inhibition of DNA synthesis by ADR was delayed in onset, and increased gradually, both at low and high drug concentrations. The data suggest that the dependence of ADR lethality on proliferation rate and the higher therapeutic ratio in plateau phase cells with prolonged drug exposure are not directly related to the ADR effects on DNA synthesis. (Author abstract) (36 Refs)

9. EVIDENCE OF COOPERATIVITY AND ALLOSTERISM IN THE BINDING OF VARIOUS ANTIBIOTICS AND CARCINOGENS TO DNA.

Rosenberg LS, Balakrishnan MS, Graves DE, Lee KR, Winkle SA, Krugh TR
Dept. Chemistry, Univ. Rochester, Rochester, NY, 14627
ACS Symp Ser; 186:269-281 1982

Studies are presented which show that the dissociation kinetics of daunorubicin, in the presence and absence of actinomycin D, reflects the synergistic interaction of the two drugs as mediated by poly(dAdT)/poly(dAdT). The interaction of a number of drugs and carcinogens with DNA was studied by optical titration and/or phase partition. (26 Refs)

10. ENHANCED CELL KILLING THROUGH THE USE OF CELL KINETICS-DIRECTED TREATMENT SCHEDULES FROM TWO-DRUG COMBINATIONS IN VITRO.

Barranco SC, May JT, Boerwinkle W, Nichols S, Hokanson KM, Schumann J, Gohde W, Bryant J, Guseman LF
Dept. Human Biological Chemistry, Univ. Texas Medical Branch, Galveston, TX, 77550
Cancer Res; 42(7):2894-2898 1982

Kinetics-directed drug treatment schedules were tested in Chinese hamster ovary cells. Ten hr after treatment with 1,2:5,6-dianhydrogalactitol (DAG) (at a dose lethal to less than 5% of the cells), a 150% enrichment of cells into the S phase of the cell cycle was observed. This blockade in S phase was reversible and was followed at 18 hr after an exposure to DAG by a 200% increase in the fraction of cells in the G2-M phases of the cell cycle. Bleomycin, known to be most effective against G2 + M cells, had the greatest effect on cell killing when administered at that time. Rapid analysis by flow microfluorometry techniques was used to determine the DAG-induced kinetics changes, thus allowing treatment with the second drugs at the most opportune time. The DAG-induced kinetics changes were also demonstrated in a line of human adenocarcinoma of the stomach in vitro and in Ehrlich ascites tumor cells in vivo. In all cases, the enrichment of cells into S phase was reversible at the doses used and was followed by a reversible blockade in G2-M. (Author abstract) (9 Refs)

11. METABOLISM AND THERAPEUTIC EFFICACY OF 9-BETA-D-ARABINOFURANOSYL-2-FLUOROADENINE AGAINST MURINE LEUKEMIA P388.

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Cancer Res; 42(7):2587-2591 1982

The biochemical basis for the differential therapeutic activity of equally toxic doses of 9-beta-D-arabinofuranosyl-2-fluoroadenine (F-ara-A) administered on two schedules to tumor-bearing mice has been studied. A single dose (234 mg/kg) of F-ara-A in solution decreased the number of P388 leukemia cells by greater than 10(3), whereas a multiple-dose regimen (41 mg/kg every day for 5 days) of equal toxicity to the host was ineffective at reducing the tumor burden. No antitumor activity was seen when an equal dose of the relatively insoluble F-ara-A was injected as a suspension. The 5'-triphosphate of F-ara-A accumulated in P388 cells in levels proportional to the dose of the nucleoside and disappeared from these cells at an exponential rate with a half-life of 2.9 hr, which was independent of the cellular concentration of the nucleotide. The extent and duration of the inhibition of DNA synthesis of P388 cells was dependent on the dose of F-ara-A, but the rates of recovery were similar and in proportion to the cellular concentration of the analog triphosphate. The extent of the inhibition of DNA synthesis in host bone marrow and intestinal mucosa was also related to the dose of F-ara-A, but the recovery of these tissues proceeded to similar, incomplete levels (less than 60% of initial) 24 hr after F-ara-A injection of either 41 or 234 mg/kg. These results suggest that the equal toxicity of the two regimens of F-ara-A may be attributed to the similar extent of inhibition of host-tissue DNA synthesis evoked by each. In contrast, the greater extent and longer duration of inhibition of P388 cell DNA synthesis caused by the single dose of F-ara-A was responsible for its superior therapeutic activity. Measurements of F-ara-A triphosphate concentrations and the DNA-synthetic capacity of tumor and host tissues are determinants of the action of F-ara-A and may be used to predict optimal therapeutic dose schedules. (Author abstract) (23 Refs)

12. ORNITHINE DECARBOXYLASE INDUCTION AND THE CYTOSKELETON IN NORMAL AND TRANSFORMED CELLS.

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J Cell Physiol; 111(2):133-139 1982

Ornithine decarboxylase (ODC) induction of normal human skin fibroblasts by colchicine (COL) and other cytoskeletal disorganizing agents was compared to that of HeLa and transformed CHO-K1 cells. Treatment with fresh medium alone was sufficient to release a large fraction of the G1 block in HeLa cells, whereas serum was required to release normal fibroblasts from G1 block. DNA synthesis in the growth arrested cells was minimal and release from G1 block was followed by initiation of ODC synthesis and subsequently of DNA synthesis in both cell lines. Induction of ODC by medium change was completely prevented in both cell lines by addition of 10 ug/ml actinomycin D (ACTD) or 25 ug/m cycloheximide (CYH). The fact that ODC activity in cells released from G1 block revealed rising and falling phases indicated that both activating and inactivating processes were involved. While increasing COL concentrations ODC induction decreased in normal fibroblasts. The curve for HeLa cells was biphasic. Vinblastine produced effects similar to those of COL. If inhibitory drugs were not added until several hr after medium change, CYH alone produced a steadily diminishing ODC activity in both cell lines. In the absence of protein synthesis, COL did not contribute any additional effect to the enzyme inactivation process. The inhibitory action of COL was probably exerted on prevention of protein synthesis rather than inactivation of already synthesized enzyme. The CHO-K1 cell line resembled HeLa cells in all respects. (30 Refs)

13. A MOLECULAR RATIONALE FOR NITROSOUREA INDUCED CYTOTOXICITY.

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INSERM Symp; 19:61-77 1981

Mechanisms of alkylation and carbamoylation of nuclear macromolecules by chlorozotocin and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, as monitored by 14C-labeling of the chloroethyl group of both drugs, are reviewed. Histone and non-histone proteins, nuclear RNA, and chromatin are discussed as target molecules for alkylation. Cytotoxicity apparently results from interaction with transcriptionally active chromatin and possibly from interaction with the nuclear protein apparatus and interference with DNA association with the nuclear matrix. (20 Refs)

14. INHIBITION OF RNA DEPENDENT DNA POLYMERASES BY ANTHRACYCLINE ANTIBIOTICS.

Bogdany L, Csanyi E
Inst. Drug Res., H-1325 Budapest, Hungary
Neoplasma; 29(1):37-42 1982

In our experimental work we intended to study the effect of certain anthracycline antibiotics, like Adriamycin, Daunomycin, Carminomycin on the RNA dependent DNA polymerase, ie reverse transcriptase (RT) system. Over the direct effect on the RT our aim was to find out the rate of selectivity of above antibiotics on the RT. For doing this we compared the above effects to those found on natural nucleic acid polymerases. These experiments were confirmed using synthetic polynucleotide template poly(rA)n(dT)12-18 for the Rauscher RT enzyme and poly(dA)n - poly(dT)n for E coli DNA polymerase I. In our work we have shown that Carminomycin, in contrast to Adriamycin and Daunomycin, possesses a highly specific inhibitory effect on the RT enzyme system. (Author abstract) (14 Refs)

15. CIRCADIAN RHYTHM IN LEWIS LUNG CARCINOMA AND ITS INFLUENCE ON CYTOSTATIC TREATMENT (MEETING ABSTRACT)

Reinecke D, Flentje M, Akokan G, Klein HO
Medical Clinic, University of Cologne, Cologne, W. Germany
Cell Tissue Kinet; 15(1):111 1982

Autoradiography, scintillation counting and flow-cytophotometry show circadian variation of tumor growth in a subcutaneously transplanted Lewis Lung Carcinoma. DNA-synthesizing activity is low at 8 am and reaches its maximum between 8 and 12 pm. This rhythm is maintained in cell culture and cannot be altered by abolition of the daily light/dark cycle. Further investigations concern growth fraction and flux rates of cells through the different cycle phases at various day and night times. Cyclophosphamide administration is most effective when given at 8 am and 8 pm; the effects of S-phase specifically active drugs will be reported, too. Furthermore, metabolism of cyclophosphamide as function of day and night time was measured in C57Bl mice. (no Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

16. METABOLIC ACTIVATION OF ADRIAMYCIN BY NADPH-CYTOCHROME P-450 REDUCTASE, RAT LIVER AND HEART MICROSOMES AND COVALENT PROTEIN BINDING OF METABOLITES.

Scheulen ME, Kappus H
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Adv Exp Med Biol; 136(partA):471-485 1982

NADPH-dependent covalent binding of adriamycin-metabolites to bovine serum albumin and microsomal proteins in an aerobic in vitro-system with isolated NADPH-cytochrome P-450 reductase, rat liver, and rat heart microsomes, respectively, is reported. The covalent binding was revealed by means of spectrophotometric identification of the anthracycline moiety of the covalently bound adriamycin-metabolites. Based on this study and others, a model for the mechanism of antineoplastic, myelosuppressive, and cardiotoxic action of adriamycin, respectively, was proposed. Two reactive intermediates are generated in a cyclic process of bioreductive activation of adriamycin and spontaneous reoxidation; semiquinone radicals of adriamycin and superoxide radicals. NADPH and oxygen are consumed at the same time. Superoxide radicals formed by reoxidation and other reactive oxygen-species generated could be responsible for the destruction of intracellular macromolecules. The semiquinone radicals of adriamycin formed by bioreductive activation are metabolized to 7-deoxy-adriamycin-aglycone. The concomitant depletion of soluble sulfhydryls like glutathione may lead to further toxic effects. The results suggest covalent protein binding of adriamycin-semiquinone radicals formed by NADPH-cytochrome P-450 reductase. Because covalent protein binding also occurred in rat heart microsomes, this biological effect may contribute to adriamycin-induced cardiotoxicity; this method of determining covalent binding of adriamycin-metabolites to cardiac protein may be a useful in vitro test system for analyzing the cardiotoxicity of new antineoplastic anthracycline antibiotics. (37 Refs)

17. THE EFFECT OF ADRIAMYCIN CARDIOTOXICITY ON ESSENTIAL TRACE METAL METABOLISM IN THE RAT HEART (MEETING ABSTRACT)

Lee BC, Stemmer KL
University of Cincinnati Medical Center, Cincinnati, OH, 45267
Toxicologist; 2(1):112 1982

Adriamycin (ADR, doxorubicin HCl) is a cardiotoxic anthracycline cancer chemotherapy agent that is suspected of interfering with essential trace metal metabolism in the heart. ADR cardiotoxicity is theorized to be a result of radical/peroxide damage. ADR generates superoxide anion radicals, which can be detoxified to H2O2 by superoxide dismutases (SODs). The essential trace metals, copper, zinc, and manganese, are associated with SODs and were examined for relationships to ADR cardiotoxicity. Weanling male Sprague-Dawley CD rats were given ADR ip 2 mg/kg bw x 9 days. Diet and environment were trace metal controlled. Cardiac CuZn-SOD, total SOD, Cu, Zn, and Mn were assayed. EKGs (electrocardiogram) and histopathology were scored. SOD was assayed in solution and in heart homogenate, with or without ADR. Whole heart Mn was significantly decreased. There were significant non-specific EKG changes, but not QRS (ventricular complex) widening. Significant histopathological changes were seen in heart, kidney, and liver. Trends indicate CuZn-SOD was increased in the heart, but total SOD was decreased. One hundred and eighty-eight x 10-6M ADR gave 50% inhibition of CuZn-SOD standard aqueous solution. ADR 3.33 x 10-8M completely inhibited total SOD in heart homogenate. (no Refs)

18. THE EFFECTS OF NITROGEN MUSTARD (HN2) ON ACTIVITIES OF THE PLASMA MEMBRANE OF PC6A MOUSE PLASMACYTOMA CELLS.

Baxter MA, Chahwala SB, Hickman JA, Spurgin GE
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Biochem Pharmacol; 31(9):1773-1778 1982

Nitrogen mustard, HN2 (10(-5) M), inhibited the transport of the potassium congener 86rubidium into PC6A mouse plasmacytoma cells by 45% after a 4 hr incubation at 37 C in vitro. HN2 (10(-3) M) had a rapid effect on the profile of 86rubidium transport into PC6A cells when added simultaneously with the 86 rubidium whereas a monofunctional analogue of HN2 ((2-chloroethyl)dimethylamine) had no effect at 10(-3) M. The transport of the amino acid analogues alpha-aminoisobutyric acid and cycloleucine into PC6A cells was inhibited by 19% and 5% respectively after a 4 hr incubation with 10(-5) M HN2. The results suggest that the activity of plasma membrane Na+K+-ATPase may be affected by HN2. This enzyme may play a pivotal role in controlling cell growth and division. Crude cell membrane preparations from PC6A cells had variable Na+K+-ATPase activity which was possibly due to contamination with mitochondrial Mg++-ATPase. Incubation of a crude cell membrane preparation in the presence of 40 nM dicyclohexylcarbodiimide gave constant Na+K+-ATPase activity which was inhibited by 44% on incubation with HN2 (10(-3) M) for 0.5 hr. The monofunctional analogue of HN2 inhibited this preparation by only 7% under the same conditions. It is suggested that inhibition of Na+K+-ATPase by HN2 may be an important facet of its cytotoxic activity. (Author abstract) (40 Refs)

19. EFFECT OF TUNICAMYCIN ON INSULIN BINDING AND ON PROTEOGLYCAN SYNTHESIS AND DISTRIBUTION IN SWARM RAT CHONDROSARCOMA CELL CULTURES.

Stevens RL, Schwartz LB, Austen KF, Lohmander LS, Kimura JH
Dept. Medicine, Harvard Medical Sch., Boston, MA, 02115
J Biol Chem; 257(10):5745-5750 1982

Tunicamycin, an inhibitor of dolichol-diphospho-N-acetylglucosamine formation and hence an inhibitor of N-linked oligosaccharide biosynthesis, suppressed total proteoglycan synthesis by Swarm rat chondrosarcoma chondrocytes without affecting the size of the proteoglycan molecule, its secretion from the cell, or its ability to be retained in the extracellular matrix. In addition, tunicamycin did not substantially alter the ability of the chondrocytes to polymerize glycosaminoglycan onto an exogenous beta-D-xyloside acceptor. A secondary effect of tunicamycin suppression of proteoglycan synthesis was that a lesser amount of newly synthesized proteoglycan diffused from the extracellular matrix into the culture medium. The ability of exogenous hyaluronic acid and proteoglycan to increase the percentage of newly synthesized 35S-proteoglycan in the medium in tunicamycin-treated cultures indicates that matrix retention of 35S-proteoglycan is related to the total extracellular uronic acid content rather than to the presence or absence of mannose oligosaccharides bound to the proteoglycan molecule. These noncytotoxic concentrations of tunicamycin (33-333 ng/ml) decreased [3H]mannose incorporation to the same extent that they decreased total [35S]sulfate and [3H]serine incorporation, and caused the chondrocyte to synthesize and secrete a species of beta-hexosaminidase that was mannose-deficient as assessed by its failure to bind to concanavalin A. The additional finding of decreased insulin binding to tunicamycin-treated chondrosarcoma chondrocytes suggested that the inhibition of proteoglycan synthesis was due to diminution of receptors which respond to stimulatory hormones. (Author abstract) (24 Refs)

20. INHIBITION OF ANTERIOR PITUITARY CYCLIC AMP PHOSPHODIESTERASE BY COLCHICINE AND VINBLASTINE.

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FEBS Lett; 141(1):25-28 1982

The inhibition of the anterior pituitary cyclic adenosine monophosphate phosphodiesterase (cAMP) by the microtubule inhibitors colchicine (COL) and vinblastine (VBL) was observed studying the possible role of the microtubules in the hormone secretion. Both alkaloids led to a significant increases in pituitary cAMP concentration as did theophylline and prostaglandin E2 that were included as positive controls. No effect of either COL (10(-3) M) or VBL (10(-4) M) upon pituitary adenylate cyclase activity was seen although prostaglandin E2 (10(-6) M) and sodium fluoride (10(-2) M) led to 2-and 4xX stimulations of the enzyme. In contrast, both alkaloids led to a concentration-dependent inhibition of the pituitary cAMP phosphodiesterase with about half-maximal effect being seen at 10(-3) M for both COL and VBL. The COL effect was seen in the presence or absence of divalent calcium (50 uM). Lumicolchicine, produced from colchicine by UV irradiation at 366 nanometers, was equipotent with COL in these studies. (16 Refs)

21. IN VITRO STUDY OF TUBULIN POLYMERIZATION: EFFECTS OF ATP, VINBLASTINE AND ISAXONINE.

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Nouv Presse Med; 11(16):1227-1232 1982

The dual action of vinblastine on tubulin, namely disruption and aggregation, is analyzed by turbidimetry. The existence of two different binding sites for the alkaloid is confirmed. The high affinity site binds vinblastine at low concentrations, at which no effect is observed on depolymerized tubulin, but where pre-formed microtubules are disrupted. The low affinity site is associated with tubulin aggregation. The binding constants of these two sites have been evaluated. Isaxonine (N-isopropyl-amino-2 pyrimidine) partially inhibits the effects of vinblastine, both on microtubule disruption and tubulin aggregation. (Author abstract) (35 Refs) (In FRE)

22. SOME EFFECTS OF MISONIDAZOLE ON CELL PROLIFERATION IN EMT6 TUMOURS (MEETING ABSTRACT)

Rockwell S
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Cell Tissue Kinet; 15(1):111 1982

The nitroimidazole, misonidazole is being examined extensively in the laboratory and clinic because it selectively sensitizes hypoxic cells to radiation and is preferentially toxic to hypoxic cells. Treatment with misonidazole produces changes in tumor cell proliferation patterns. Some of these result from the selective cytotoxicity of the drug and the resulting changes in the environment and population structure of the viable tumor cells. Misonidazole also produces a number of physiologic changes in the host (such as the marked and prolonged hypothermia induced in mice by high doses) which may lead to changes in cell proliferation. Misonidazole also has direct effects on cell proliferation: at concentrations similar to those obtainable in mouse tumors, it perturbs the growth and population structure of well-oxygenated monolayers in vitro. (no Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

23. BIOCHEMICAL BASIS FOR IMPAIRED DRUG METABOLISM IN TUMOR-BEARING RATS EVIDENCE FOR ALTERED REGULATION OF HEPATIC MICROSOMAL HEMEPROTEIN SYNTHESIS.

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Biochem Pharmacol; 31(8):1535-1543 1982

The pharmacologic effects of many drugs are enhanced in animals bearing tumors. This apparently stems from a decrease in the microsomal metabolism of these compounds in liver cells, owing to a decrease in either the activities of certain enzymes or in the content of cytochrome P-450 in microsomes, or both. Since impaired drug metabolism may have a direct bearing on the outcome of chemotherapy, a study of the biochemical basis for this alteration was begun. In female Sprague-Dawley rats bearing Walker 256 solid tumors im, pentobarbital metabolism was impaired as judged from prolonged sleeping-times. This effect was accompanied by a decrease in the microsomal content of cytochrome P-450. Analysis of hepatic microsomes by sodium dodecylsulfate-polyacrylamide gel electrophoresis revealed that a microsomal protein of approx 53,000 daltons was diminished in livers of tumor-bearing animals when compared to normal controls. When rats were injected with [3H]leucine, approx 40% less 3H was associated with the microsomal proteins in the cytochrome P-450 region of tumor-bearing animals than with those of normal controls. This was attributed to a decrease in the rate of synthesis of these, but not of other, microsomal proteins. The overall content of microsomal hemeproteins of tumor-bearing rats was reduced considerably, when compared to normal controls. We found that in the livers of 7-day tumor-bearing rats, the activity of delta-aminolevulinic acid synthetase was only 16% of control activity; conversely, the activity of hepatic microsomal heme oxygenase in the tumor-bearing rats was nearly 8x greater than that of the normal animals. Together, these data indicate that perturbations in heme- and hemeprotein-synthesis caused the reduced content of cytochrome P-450 seen in tumor-bearing rats, and they provide partial explanation for diminished drug metabolism by hepatic microsomes in the presence of a growing, transplantable, non-hepatic tumor. (54 Refs)

24. THE MECHANISMS OF CYTOTOXICITY AND CHEMOSENSITIZATION BY MISONIDAZOLE AND OTHER NITROIMIDAZOLES.

Brown JM
Div. Radiobiology Res., Dept. Radiology, Stanford Medical Center, Stanford, CA, 94305
Int J Radiat Oncol Biol Phys; 8(3/4):675-682 1982

Basic observations on the hypoxic cell cytotoxicity of misonidazole (shape of the curve, importance of electron affinity, temperature dependence, formation and intracellular binding of reduced products, production of DNA damage and influence of prior irradiation, effect on glycolysis, and effect on nonprotein thiols, particularly glutathione) are reviewed. A model for MISO cytotoxicity is proposed. Topics discussed in relation to MISO chemosensitization include the following: in vitro preincubation effect, in vivo chemosensitization, selective killing of hypoxic cells by MISO, changes in the pharmacokinetics of drugs induced by MISO, and a manifestation of the in vitro effect. (44 Refs)

25. ENHANCEMENT OF CYTOTOXIC DRUGS BY MISONIDAZOLE (MISO) IN LEWIS LUNG TUMORS OF DIFFERENT SIZES, AND MOUSE BONE MARROW.

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Int J Radiat Oncol Biol Phys; 8(3/4):643-646 1982

The role of radiobiologically hypoxic cells in the enhancement of the cytotoxicity of melphalan (L-PAM), cyclophosphamide (CYC), and 5-fluorouracil (5FU) by misonidazole (MISO) was examined. Dose-response curves were determined for L-PAM, CYC, and 5FU administered alone and simultaneously with MISO using four different experimental systems: 250 mg im Lewis lung carcinomas, less than 2 mg lung colonies, in situ single tumor cells in pulmonary capillaries, and normal bone marrow colony forming units. Male and female C57Bl/Cbi mice were used. MISO enhancement was much greater in im tumors with survival curve slope ratios (SR) of 1.6-1.9 than in any of the other systems with SR of 1.0-1.3. For im tumors and 2 mg lung colonies, proportions of radiobiologically hypoxic cells also were assessed by constructing radiation dose-survival curves under air-breathing and fully hypoxic conditions, and measuring extent of displacement of the hypoxic part of the curve. Im tumors contained 15% of hypoxic cells and small lung colonies contained less than 1% or radiobiologically hypoxic cells. The results indicated that hypoxia is important for MISO enhancement of cytotoxic drug action. (10 Refs)

26. REPAIR OF DOUBLE STRAND BREAKS IN X-IRRADIATED EHRLICH ASCITES TUMOUR CELLS AND THE EFFECTS OF THE DNA INHIBITOR BETA-ARA A (MEETING ABSTRACT)

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Molecular and Cellular Mechanisms of Irradiation, March 17-19, 1982, Neuherburg, W. Germany. Gesellschaft fur Strahlen und Umweltforschung MBH 65 pp., 1982.

The repair of DNA dsb has been followed in cells after x-irradiation using the unwinding and the neutral sucrose centrifugation methods. Dsb, induced with a frequency of 40 dsb/cell/Gy, repaired with a time constant t37 equals 2-4h. Beta-ara A strongly inhibited dsb repair; the inhibition was complete at about C equals 400 umol/l. Experiments designed to simulate the procedure used in plating of cells to measure survival, showed that when Beta-ara A was washed away from cells after treatment, the repair of dsb returned. Beta-ara A has been shown to remove the shoulder from the survival curve of this cell line (Iliakis 1980), therefore it was of interest to measure the breaks remaining at longer times following irradiation. Although repair of dsb returned after washing away the drug, it was found that more breaks persisted in Beta-ara A treated cells than in the control untreated cells. A larger number of dsb were also measured at times corresponding to the time of first cell division, in lightly irradiated cells. These additional dsb may contribute to the increased yield of chromosome aberrations observed, after irradiation and Beta-ara A treatment, at first mitosis which probably cause the increased cell killing observed. It is postulated however that an increased level of misjoining of DNA strands also contributes to the increased aberration formation seen after Beta-ara A treatment of irradiated cells. (2 Refs)

27. EFFECT OF ELECTRON AFFINIC HYPOXIC CELL SENSITIZERS ON THE RADIOLYTIC DEPLETION OF OXYGEN IN MAMMALIAN CELLS IRRADIATED AT ULTRAHIGH DOSE RATES.

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Int J Radiat Oncol Biol Phys; 8(3/4):427-430 1982

A radiation chemical mechanism is proposed for the prevention of the breaking survival curve by electron affinic sensitizers, by interference with oxygen depletion. Sensitizers that were investigated included misonidazole (Ro-07-0582), metronidazole, Ro-05-9963, nitrofurazone, nifurpipone, and diamide. Breaking survival curves were determined with cells equilibrated with 0.44% O2 and irradiated with 3 nanosec electron pulses. Based on the data, it is hypothesized that the sensitizer acts by competing with oxygen for the radiation-induced intracellular oxygen-binding species, perhaps a hydrated electron adduct, leaving oxygen free to participate in radiosensitization reactions during the lifetime of the oxygen-sensitive radiation-induced target sites for lethal damage, probably DNA radicals produced by hydroxyl radical attack. The proposed role of the sensitizer in the interference with oxygen depletion is a transient phenomenon, occurring on the microsecond to millisecond time scale. (12 Refs)

28. REVERSAL BY ISAXONINE OF THE INHIBITORY EFFECT OF VINCRISTINE ON THE GROWTH OF NEURITES IN CULTURES.

Tarrade T

LA 204, CESN, CNRS, F 91190 Gif-sur-Yvette, France

Nouv Presse Med; 11(16):1233-1237 1982

It has been previously demonstrated that isaxonine increases neurite elongation of dorsal root ganglia in vitro. In purpose to demonstrate that this effect results of an action at the level of the cellular cytoskeleton, we have studied effects of isaxonine on neurite elongation inhibited by vincristine sulfate which is known to bind specifically on tubulin and consequently perturb microtubule assembly. Neurite elongation of dorsal root ganglia cultivated with vincristine (0.5 or 10-10M) is compared to neurite elongation of ganglia cultivated with vincristine plus isaxonine (10 7-10 1M). Results show that isaxonine prevents, at least partially, the effect of vincristine. The protective effect observed in vivo in the rat and in the human seems to indicate that isaxonine acts at the level of microtubules of nerve fiber. (Author abstract) (12 Refs) (In FRE)

29. PARADOXICAL EFFECT OF 1-BETA-D-ARABINOFURANOSYL CYTOSINE TRIPHOSPHATE ON BLEOMYCIN-INDUCED UNSCHEDULED DNA SYNTHESIS IN PERMEABLE SARCOMA CELLS.

Seki S, Iwamoto H, Maki Y, Oda T

Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., 2-5-1, Shikata-cho, Okayama 700, Japan

Experientia; 38(6):657-658 1982

The compound, 1-beta-D-arabinofuranosyl cytosine-5'-triphosphate (araCTP), an inhibitor of DNA synthesis, paradoxically enhanced unscheduled DNA synthesis (USD) induced by bleomycin in permeable mouse sarcoma cells. A greater enhancing effect of araCTP on bleomycin-induced USD was observed with lower concentrations of dCTP in the assay mixture. USD measured without bleomycin in nuclei isolated from mouse sarcoma cells was not enhanced, but inhibited by araCTP. (Author abstract) (15 Refs)

30. THE EFFECT OF THIAMINE AND THIAMINE PYROPHOSPHATE ON ACTION OF 5-FLUOROURACIL ON NUCLEIC ACID SYNTHESIS.

Aksoy M
Sch. Nutrition and Dietetics, Hacettepe Univ., Ankara, Turkey
Kanser; 11(1):41-54 1981

Treatment of rats with 5-fluorouracil (5-FU) in the presence of thiamine did not impair the effect of the drug on deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein content of the liver, spleen and kidney whereas thiamine pyrophosphate (TPP) appeared to reduce cytotoxic effect of the drug on liver DNA. This reduction could be due to protection of normal tissue by TPP. (Author abstract) (25 Refs)

31. CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE-DEPENDENT PROTEIN PHOSPHORYLATION AND THE CONTROL OF LEUKEMIA L1210 CELL GROWTH.

Mednieks MI, Jungmann RA, DeWys WD
Lab. Biological Structure, Natl. Inst. Dental Res., Building 30, Room 211, Bethesda, MD, 20205
Cancer Res; 42(7):2742-2747 1982

Synergistic increases in the survival of mice bearing an L1210 leukemia tumor have been demonstrated previously after treatment with 1,3-bis(2-chloroethyl)-1-nitrosourea together with theophylline over those treated with either agent alone. These results imply that manipulation of cyclic adenosine 3':5'-monophosphate (cyclic AMP) levels in L1210 cells may result in alteration of sensitivity to chemotherapy and alterations in tumor growth. In the present study, we have shown that in vivo treatment of L1210 cells with theophylline results in changes in intracellular cyclic AMP-dependent protein kinase activity levels as well as in an apparent redistribution of both the nuclear and cytoplasmic isozymes. Biochemical events in the tumor cells immediately after administration of theophylline in vivo or a cyclic AMP analog (8-parachlorophenylthio cyclic adenosine 3':5'-monophosphate) in vitro were independent of the presence of 1,3-bis(2-chloroethyl)-1-nitrosourea. The changes apparently involve signal transduction via the adenylate cyclase system and manifest as: (a) increased sensitivity of cyclic AMP-dependent protein kinase to activation by cyclic AMP after treatment of L1210 cells with theophylline; (b) decrease in endogenous nuclear protein phosphorylation sites; and (c) protein kinase isozyme redistribution between nuclear and extranuclear compartments, ie, a relative increase of the Type I isozyme activity in the nuclear and of the Type II isozyme activity in the 900 x g supernatant fractions after treatment of the mice of theophylline. The relative activity increases are accompanied by relative decrease of Type II activity from the nucleus and Type I isozyme activity from the 900 x g extranuclear supernatant fraction. These events appear temporally related to changes in nuclear RNA metabolism as evidenced by altered kinetics of RNA precursor uptake and incorporation into tumor cell RNA after treatment. These results imply that the cyclic AMP-dependent phosphorylative modification of intracellular proteins may play a regulatory role in tumor cell growth and in theophylline-mediated tumor regression. (Author abstract) (42 Refs)

32. AUGMENTATION OF THE INTRACELLULAR LEVELS OF POLYGLUTAMYL DERIVATIVES OF METHOTREXATE BY VINCRISTINE AND PROBENECID IN EHRLICH ASCITES TUMOR CELLS.

Fry DW, Yalowich JC, Goldman ID
(c/o Goldman) Dept. Medicine, Medical Coll. Virginia, Richmond, VA, 23298
Cancer Res; 42(7):2532-2536 1982

The intracellular accumulation of poly-gamma-glutamyl derivatives of methotrexate was evaluated in the presence of vincristine or probenecid (agents which raise the intracellular level of free methotrexate) in Ehrlich ascites tumor cells. The results show that both intracellular methotrexate and its metabolites are increased by these agents and that, in the presence of L-glutamine, polyglutamate derivatives are increased by a higher percentage than is methotrexate. From 1 to 50 uM vincristine increased the levels of polyglutamate derivatives from 25 to over 300%, whereas methotrexate was raised from 25 to 80%. Similarly, 50 to 200 uM probenecid increased methotrexate polyglutamate derivatives from 31 to 88%, whereas methotrexate was raised from 0 to 30%. A determination of the bound fraction of drug indicated that the proportion of dihydrofolate reductase bound with methotrexate polyglutamates increased in the presence of these agents. Efflux studies showed that over 90% of the large pools of intracellular methotrexate polyglutamates produced by these agents was retained for at least 1 hr in the absence of extracellular methotrexate, whereas the majority of intracellular methotrexate exited the cell. These studies (a) indicate that vincristine and probenecid may be potentially useful for selectively increasing methotrexate polyglutamates in tumor cells and (b) introduce another basis for synergism observed between alkaloids and methotrexate. (Author abstract) (25 Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

33. INHIBITION OF URIDINE TRANSPORT THROUGH SARCOMA-180 CELL MEMBRANE BY ANTHRACYCLINE ANTIBIOTICS.

Choudhury SR, Deb JK, Choudhury K, Neogy RK
Dept. Biochemistry, Chittaranjan Natl. Cancer Res. Centre, 37, S.P. Mukherjee Road, Calcutta-700 026, India
Biochem Pharmacol; 31(9):1811-1814 1982

Effects of adriamycin (ADR), nogalamycin (NG), and 7-OMEN on active transport of small precursor molecules through sarcoma-180 ascites tumor cell membrane were examined. NG and ADR inhibited uptake of 3H-uridine (3H-U) by sarcoma-180 cells following an initial lag period. When NG, ADR, or 7-OMEN was preincubated with cells prior to addition of uridine, each antibiotic exhibited dose-dependent inhibition of 3H-U uptake; the effect of NG was more pronounced than that of ADR or 7-OMEN. Acid-soluble extracts from sarcoma-180 cells labelled with 3H-U at 20 C in the presence and absence of NG were subjected to chromotography to separate different uridine nucleotides. No difference in the relative distribution of radioactivity was observed among various nucleotides in control and drug-treated cells. Inhibition by NG and ADR appeared to be non-competitive. The antibiotics seemed to act by binding at a site different from the uridine binding site of the carrier protein. Inhibition of 2-deoxy-glucose uptake by sarcoma-180 cells was observed in the presence of NG and

ADR. Although DNA intercalation and subsequent inhibition of transcription is apparently the primary mode of inhibition by the anthracycline antibiotics, cellular toxicity of the antibiotics may result partially from alteration of transport properties of the cellular plasma membrane. (29 Refs)

34. METABOLIC ACTIVATION OF TRIAZENE CYTOSTATICS.

Kolar GF, Wildschutte M
Inst. for Toxicology and Chemotherapy, German Cancer Res. Centre, Heidelberg, W. Germany
Adv Exp Med Biol; 136(partB):1285-1296 1982

Metabolic activation of 1-(2,4,6-trichlorophenyl)-3,3-dimethyl-triazene (DIC) and 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC) was studied in adult male Sprague-Dawley rats. Following sc administration of DIC, a single urinary metabolite with an intact diazoamino structure was detected. The lability of the metabolite pointed to the conjugation through an O-glycosidic bond between glucuronic acid and an 3N-hydroxymethyl group, introduced by metabolic oxidation of one of the 3N-methyl groups of the triazene side-chain. The final 3N-hydroxymethyl-O-glucuronide structure came from field desorption mass spectrometry which established the molecular ion of the metabolite in agreement with the proposed structure. Thin-layer chromatographic examination of urinary excretion products from rats that had been dosed with DTIC confirmed the presence of both previously identified metabolites 5-aminoimidazole-4-carboxamide and 2-azahypoxanthine. The chromatograms also showed the presence of another metabolite with an intact diazoamino group in the molecule. The metabolite was identified as 5-(3-hydroxymethyl-3-methyl-1-triazeno)imidazole-4 carboxamide. Results indicated that enzymic oxidation of 3N-methyl to 3N-methylol sufficiently increased the solubility of the drug so that conjugation with water-soluble endogenous compound does not occur. The formation of 3N-methylols may be an important contributory factor to the broad spectrum of antineoplastic activity of triazene cytostatics. (15 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

35. EFFECT OF AMINO-SUBSTITUTED ANTHRAQUINONES ON CELL CYCLE KINETICS AND SURVIVAL (MEETING ABSTRACT)

Kimler BF, Cheng CC, Barnes RE, Barnes ML
Department of Radiation Therapy, University of Kansas Medical Center, Kansas City, KS, 66103
Cell Tissue Kinet; 15(1):104 1982

A number of anthraquinones substituted with amino-alkylamino side chains have been designed, synthesized, and tested for cytotoxicity so as to develop a relationship between chemical structure and biological activity. For cell lethality, there is a consistent correlation between cytotoxic efficacy and the presence of a particular triangular arrangement of 1 nitrogen atom and 2 oxygen atoms. The most active of the compounds is DHAQ, a dihydroxy-bis(amino-alkylamino)anthraquinone, which is approx 10 x more effective than Adriamycin. The same relative efficiency exists for the inhibition of DNA synthesis and the blockade of cell cycle progression in the G2 phase. However, the cell cycle age-responses for survival differ: DHAQ is most effective in G1, Adriamycin in S. Thus, different functional groups may be responsible for the various effects that these agents and other anthraquinones have on metabolic synthesis, cell cycle progression, and survival of cultured mammalian cells. (no Refs)

36. SYNTHESIS AND BIOLOGICAL EVALUATION OF SPARSOMYCIN ANALOGUES (MEETING ABSTRACT)

Boots MR, Duke SS, Munson AE
Departments of Pharmaceutical Chemistry and Pharmacology, Virginia Commonwealth University, Richmond, VA
129th APLA Annual Meeting, April 24-29, 1982, Las Vegas, Nevada. American Pharmaceutical Association and Academy of Pharmaceutical Sciences 101 pp., 1982.

Sparsomycin possesses a broad spectrum of biological activity including antitumor, antifungal, and antibacterial properties. In an effort to expand the structure-activity relationships for sparsomycin, several analogues were prepared and evaluated as inhibitors of protein synthesis using bone marrow cells, P388 lymphoma cells, and P815 mastocytoma cells. The analogues were designed to elucidate (1) the effect on activity of replacing the mono-oxodithioacetal side chain of sparsomycin with hydrophobic groups and (2) the requirement for a hydroxymethyl group. Replacement of the mono-oxodithioacetal side chain by a 4-substituted phenyl system afforded active compounds with the 4-bromophenyl analogue being the most active. In general, the analogues containing a hydroxymethyl group were more active in the P388 lymphoma and P815 mastocytoma cell systems. (no Refs)

37. POTENTIAL ANTICANCER AGENTS. XXIV. PHYSICO-CHEMICAL AND BIOLOGICAL INVESTIGATION OF SOME NEW ALIPHATIC AND CYCLOALIPHATIC NITROSOUREAS.

Baracu I, Botez G, Denes R, Dobre V, Ureche B, Craescu T, Voiculet N, Niculescu-Duvaz I
(c/o Niculescu-Duvaz), Oncological Inst., Bd. 1 Mai 11, Bucharest, Romania
Rev Roum Biochim; 18(3):175-190 1981

The physicochemical and biological properties of 22 new aliphatic and cycloaliphatic compounds were investigated in order to obtain data concerning their mechanism of action. Good correlations were found in a series of seven di-N-(2-chlorethyl)-N'-nitrosoureas between their antileukemic activity and both lipophilicity and alkylating capacity. These results support the assumption that DNA alkylation is responsible for the antitumor effectiveness of the agents. (43 Refs)

38. NEW RIBONUCLEOTIDE REDUCTASE INHIBITORS POSSESSING ANTITUMOR ACTIVITY (MEETING ABSTRACT)

Elford HL, Van't Riet B, Wampler G, Robertson RH, Elford RM
Virginia Associated Research Campus, Newport News, VA, 23606
Med Pediatr Oncol; 10(1):102 1982

A newly developed series of mammalian ribonucleotide reductase inhibitors based on the polyhydroxy or polyamino aromatic ring structure has proven to be an effective anticancer agents in model animal test systems. These compounds are effective ribonucleotide reductase inhibitors (u molar range) and several possess antitumor activity if there are adjacent hydroxy or amino groups on the aromatic ring. These polyhydroxy agents appear to inhibit cell replication through their effect on ribonucleotide reductase and DNA synthesis, since levels that inhibit cell replication and DNA synthesis do not affect RNA or protein synthesis or several other enzymes involved in DNA synthesis. The mechanism of action of the polyhydroxybenzoic acid derivatives appears to be related to their ability to destroy a stable free radical (diphenylpicrylhydrazyl), since there is a good correspondence between reductase inhibition and free radical destruction. The free radical trapping ability increases with the number of adjacent hydroxyl groups on the phenyl ring. Two adjacent hydroxyl groups are ten-fold more potent than the dihydroxy non adjacent compounds. A third adjoining substitution increases activity still further. The relationship between the polyhydroxy benzoic acids, esters, amides and hydroxamic acids was similar to the inhibitory exhibited by these compounds against ribonucleotide reductase. Although these compounds are metal chelators, metal chelation is unlikely as the primary mechanism of inhibition, since there is no significant differences between mono, di and trisubstituted benzohydroxamic acids to complex Fe + + +. In addition, iron salts can only partially protect against inhibition. (no Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

39. A NEW CLASS OF NITROSOUREAS. III. SYNTHESIS AND ANTITUMOR ACTIVITY OF 3,3-DISUBSTITUTED-1-(2-CHLOROETHYL)-1-NITROSOUREAS HAVING AN ARABINOPYRANOSYL, XYLOPYRANOSYL OR RIBOPYRANOSYL MOIETY.

Morikawa T, Ozeki M, Umino N, Kawamori M, Arai Y, Tsujihara K
(c/o Tsujihara) Res. Laboratories, Tanabe Seiyaku Co., Ltd., 2-2-50 Kawagishi, Toda-shi, Saitama 335, Japan
Chem Pharm Bull (Tokyo); 30(2):534-543 1982

Synthesis and antitumor activity of a new class of 3,3-disubstituted-1-(2-chloroethyl)-1-nitrosoureas bearing an aldopentose moiety such as L- or D-arabinose, D-xylose, or D-ribose are described. The glycopyranosylnitrosoureas were tested for antitumor activity against leukemia L1210 and Ehrlich ascites carcinoma by methods previously described. These nitrosoureas appear to be activated nonenzymatically by attack of the hydroxyl group of the sugar moiety on the carbonyl group to give the cyclic carbamate and had large therapeutic ratios against leukemia L1210 and Ehrlich ascites carcinoma. (7 Refs)

INTERFERON AND OTHER ANTIVIRALS

40. INTERFERON INCREASES HLA SYNTHESIS IN MELANOMA CELLS: INTERFERON-RESISTANT AND -SENSITIVE CELL LINES.

Basham TY, Bourgeade MF, Creasey AA, Merigan TC
Div. Infectious Diseases, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Proc Natl Acad Sci USA; 79(10,part1):3265-3269 1982

We report that human leukocyte interferon preparations increase the expression of beta2-microglobulin by 100-200% on the surface of normal fibroblast and melanoma cell lines sensitive to interferon. This increase in expression can be correlated with an increase in HLA synthesis as measured by incorporation of [35S]methionine in these antigens. This enhanced HLA synthesis, which is 5-to 17-fold, is time dependent and dose related. Synchronized cells in the G0/G1 phase of the cell cycle appear to be more sensitive to this interferon action. Neither an increase in surface expression nor in HLA synthesis is observed in a melanoma cell line resistant to the antiviral and antigrowth effects of interferon. Furthermore, there appears to be a stronger correlation between this increased HLA synthesis and the antiviral function that between it and the antiproliferative action of interferon. (Author abstract) (18 Refs)

41. INTERFERON-DEPENDENT INDUCTION OF MRNA FOR THE MAJOR HISTOCOMPATIBILITY ANTIGENS IN HUMAN FIBROBLASTS AND LYMPHOBLASTOID CELLS.

Fellous M, Nir U, Wallach D, Merlin G, Rubinstein M, Revel M
Institut Pasteur, Paris, France
Proc Natl Acad Sci USA; 79(10,part1):3082-3086 1982

In human cells treated with interferons, there is an increase in the amount of HLA-A,B,C and beta2-microglobulin exposed on the cell surface. We have used a cloned HLA-A,B,C cDNA probe to demonstrate by molecular hybridization that this effect of interferon is preceded by a large increase in the amount of HLA mRNA in the cell. This effect was found in five different human cell lines, with purified leukocyte and fibroblast interferons. The increase in HLA mRNA is comparable in its kinetics and dose-response to the induction of (2'-5') oligo(A) synthetase mRNA by interferons. Therefore, interferons seem to activate at least two cellular genes which have different biochemical functions. (Author abstract) (51 Refs)

42. SYNTHESIS OF (2'-5')OLIGOADENYLATE AND ACTIVATION OF AN ENDORIBONUCLEASE IN INTERFERON-TREATED HELA CELLS INFECTED WITH REOVIRUS.

Nilsen TW, Maroney PA, Baglioni C
(c/o Baglioni) Dept. Biological Sciences, State Univ. New York at Albany, Albany, NY, 12222
J Virol; 42(3):1039-1045 1982

Treatment with interferon protected HeLa cells from infection with reovirus. This virus apparently activated an antiviral mechanism that was detected by the presence of (2'-5')oligoadenylate [(2'-5')An] in intact cells. The (2'-5')An was previously shown to activate an endoribonuclease, RNase L. We measured (2'-5')An by a sensitive competition-binding assay in cells infected at different multiplicities and for different lengths of time. Nanomolar concentrations of (2'-5')An were detected in cells infected at a multiplicity of greater than 5 after 2 hr of infection, the time at which the infecting virions were uncoated. The level of (2'-5')An increased up to 6 hr postinfection but declined afterward. To establish whether viral mRNAs were cleaved by RNase L, we analyzed the RNA extracted from infected cells by a highly specific hybridization assay on Northern blots. Full-sized reovirus mRNAs were detected in control infected cells, but not in interferon-treated infected cells, at 6 hr postinfection. At this time, a nuclease activity could be detected in these cells by demonstration of cleavage of rRNA, degradation of cellular mRNA, and polysome breakdown in the presence of emetine. Since this inhibitor freezes ribosomes, cleavage of mRNA between ribosomes could only be accounted for by an endonuclease, presumably RNase L. (Author abstract) (24 Refs)

43. CONTROL OF THE PPP(A2'P)NA SYSTEM IN HELA CELLS. EFFECTS OF INTERFERON AND VIRUS INFECTION.

Silverman RH, Cayley PJ, Knight M, Gilbert CS, Kerr IM
Dept. Pathology, Uniformed Services Univ. Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20205
Eur J Biochem; 124(1):131-138 1982

HeLa cells have an unusually high level of ppp(A2'p)nA synthetase (n = 2 to greater than or equal to 4) even in the absence of interferon treatment. In accord with this ppp(A2'p)nA and ppp(A2'p)nA-mediated ribosomal RNA cleavage occur naturally in response to encephalomyocarditis virus infection in control as well as in interferon-treated cells. Despite this, in the absence of interferon treatment, encephalomyocarditis virus grows well in these cells. A possible explanation for this paradox is that the ppp(A2'p)nA dependent RNase is lost or inactivated at later times post-infection in control but not in interferon-treated cells. It appears, therefore, to be the prevention by interferon of the virus-mediated inhibition of the ppp(A2'p)n-dependent nuclease rather than the absolute level or induction of the ppp(A2'p)nA synthetase which is crucial for the activity of the ppp(A2'p)nA system in HeLa cells. These results provide evidence for a further level of control in the ppp(A2'p)nA system and show that limited ppp(A2'p)nA-mediated ribosomal RNA cleavage alone is not sufficient to cause an inhibition of virus growth. (Author abstract) (33 Refs)

44. INHIBITION OF MOUSE FIBROBLAST INTERFERON BY GANGLIOSIDES. DIFFERENTIAL EFFECTS ON BIOLOGICAL ACTIVITY AND ON INDUCTION OF (2'-5')OLIGOADENYLATE SYNTHETASE.

Krishnamurti C, Besancon F, Justesen J, Poulsen K, Ankel H
Dept. Biochemistry, Medical Coll. Wisconsin, Milwaukee, WI, 53226
Eur J Biochem; 124(1):1-6 1982

Gangliosides are potent inhibitors of the antiviral activity of mouse fibroblast and other beta-interferons. We have compared the effects of gangliosides on antiviral and antigrowth activities of mouse fibroblast interferon and on the induction of (2'-5')oligoadenylate synthetase, one of the enzymes implicated in the antiviral state induced by interferon. Whereas both biological effects appear to be inhibited by gangliosides in an analogous fashion, inhibition of induction of (2'-5')oligoadenylate synthetase does not correlate with inhibition of vesicular stomatitis virus replication. Ganglioside concentrations that inhibit the interferon-induced (2'-5')oligoadenylate synthetase to levels close to those of uninduced cells, still allow for a 100-1,000-fold reduction of viral yield. Significantly higher ganglioside concentrations are required to prevent completely the antiviral effect. This biphasic relationship between (2'-5')oligoadenylate synthetase levels and inhibition of viral yield suggests that no or very small increases in synthetase levels are involved in inhibition of virus by between two and three orders of magnitude. (Author abstract) (35 Refs)

45. SENSITIVITY AND RESISTANCE OF HUMAN TUMOUR CELLS TO INTERFERON AND RINRCN.

Lin SL, Greene JJ, Ts'o PO, Carter WA
Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Nature; 297(5865):417-419 1982

The antiproliferative effects of interferon (IFN) and double stranded (ds)RNA on human HT1080 fibrosarcoma and RT4 epidermal carcinoma cell lines were characterized using Luria-Delbruck fluctuation analysis of IFN resistance (IFNr). Examination of isolated colonies derived from resistant populations revealed that IFNr cells possess the same population doubling times in the presence and absence of IFN at concentrations normally resulting in complete cessation of growth. Consistent with the idea that IFNr is an induced trait, resistant colonies reverted to a sensitive state after varying lengths of time. In the resistant state, cells were at least as sensitive as their parental populations to the antiviral effects of IFN when vesicular stomatitis virus was used as the challenge virus, suggesting that resistance to the antiproliferative effects of IFN does not necessarily correlate with changes in sensitivity to its antiviral effects. The sensitivities of the IFNr lines to the antiproliferative effects of the synthetic dsRNA, rInrCn, were characterized. Resistant lines of both HT1080-2 and RT4-1 clones displayed the same sensitivity to rInrCn-mediated toxicity as did their respective parental HT1080-2 and RT4-1 lines. Luria-Delbruck analysis indicated that the INFr trait is a non-randomly acquired phenotype probably induced by IFN at the time of selection. The IFNr cells retain sensitivity to the antiviral effects of IFN, as well as to the antiproliferative effects of dsRNA. (24 Refs)

46. AUGMENTATION OF MOUSE NATURAL KILLER ACTIVITY BY INTERFERON.

Satomi H, Barn S, Yamagiwa T, Kato K, Tsuneoka H, Sakakida K, Imanishi J, Kita M, Oku T, Kishida T

Dept. Orthopedics, Kyoto Prefectural Univ., Kyoto, Japan

Nippon Seikeigeka Gakkai Zasshi; 55(9):1104-1105 1981

Treatment with interferon (IFN), both in vitro and in vivo increased the activity of natural killer (NK) cells, reaching a maximum at 12 hr after in vivo treatment. The increase was proportional to the IFN doses. Transplantation of Dunn's osteogenic sarcoma increased the NK activity, which, however, was low in tumor-bearing C3H/HeJ mice. The IFN treatment enhanced the NK activity in tumor-bearing mice, suggesting that the increase in the NK activity is a factor in the antitumor effect of IFN. (no Refs) (In JPN)

47. SENSITIVITY OF CULTURED HUMAN OVARIAN CARCINOMA CELLS TO INTERFERONS OF DIFFERENT ORIGIN.

Timofeev IV, Krispin TI, Shloma DV

N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR

Vopr Virusol; (2):228-230 1982

Antiproliferative effect of human, porcine, and bovine interferons (IF) was studied in cultured cells of human ovarian carcinoma (OC). Both homologous and heterologous (porcine) IF produced concentration-dependent inhibition of DNA biosynthesis in OC cells (18.2-50.5% and 18.2-68.4%, respectively). Bovine IF caused less marked inhibition of proliferative activity (6.6-43.6%). (8 Refs) (In RUS)

OTHER RELATED STUDIES

48. POLYMERS FOR POTENTIAL CANCER THERAPY: A BRIEF REVIEW.

Gebelein CG
Dept. Chemistry, Youngstown State Univ., Youngstown, OH, 44555
ACS Symp Ser; 186:193-203 1982

The polymeric drug approach to the treatment of antineoplastic diseases is reviewed. A polymeric drug is a polymer that contains a drug unit either as part of the polymer backbone, as a terminal group, or as a pendant unit off the polymer backbone. The rationale for the use of polyanionic polymers (PP) probably arises from the fact that such compounds include biologically active substances such as heparin and DNA. Statalon is a polysaccharide PP with activity against many experimental cancers. Another agent in this group is maleic anhydride copolymer (DIVEMA). A number of polymers incorporate a nucleic base unit on the polymer chain. Such polymers have been described which contain 5-fluorouracil and 6-mercaptopurine (6-MP). The methylthio derivative of 6-MP is a water soluble polymer that forms complexes with uracil containing polymers, but no biological data has been reported. Other active polymers have been prepared which generally incorporate a known antineoplastic compound attached to the polymer chain as a pendant group. Such polymers involve methotrexate, adriamycin, and cis-dichlorodiammineplatinum II. At the present time, it is not possible to state which polymeric system(s) will eventually prove to be the most useful in cancer therapy, but a directed PP would be most useful. (65 Refs)

49. ANTITUMOR EFFECT OF XENOGENIC SUBSTANCES IN VIVO AND IN VITRO.

Munder PG, Stiefel T, Widmann KH, Theurer K

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Onkologie; 5(2):98-104 1982

The proliferation of various tumor cells was inhibited in vivo and in vitro after application of/or incubation with xenogeneic liver tissue. The development of sc-implanted meth-A-sarcoma was blocked by the prophylactic injection of these preparations. In addition firmly established tumors regressed under therapy. Preparations obtained from xenogeneic organs like thymus, placenta or brain had a similar antitumor activity. A mixture of various xenogeneic tissues from different species had a much higher therapeutic efficiency. In the Meth-A-system the xenogeneic material surpassed the antineoplastic effect of rather high doses of cyclophosphamide. The preparations showed no side-effects in mice and rats. These results were supported by experiments in tissue culture. This new antitumor activity of xenogeneic tissues in vivo is interpreted as mediated by an increased host defense. The results in tissue culture however, indicate also a direct regulatory effect on cells. (Author abstract) (18 Refs) (In GER)

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ANTITUMOR AND ANTIVIRAL AGENTS

Mechanisms of Action

SERIES CB19 No. 82/11

NOVEMBER, 1982

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EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. INTERACTION OF ADRIAMYCIN WITH DNA AS STUDIED BY RESONANCE RAMAN SPECTROSCOPY.

Manfait M, Alix AJ, Jeannesson P, Jardillier JC, Theophanides T
Lab. Recherches Optiques, Faculte des Sciences, B.P. 347, 51062 Reims, France

Nucleic Acids Res; 10(12):3803-3816 1982

Raman and resonance Raman spectra of the complex DNA-adriamycin in aqueous solution have been recorded and analyzed. Calf thymus DNA was used and it is found that in the complex DNA-adriamycin the chromophore of adriamycin is intercalated in the GC sequences. The substituents on the rings give hydrogen bonding interactions with the base pairs above and below the intercalation site. It is suggested from the Raman and resonance Raman spectral modifications that the phenolic groups of the chromophore are involved in the drug-DNA intercalation, in addition to pi-pi, hydroxyl and amino group interactions. (Author abstract) (25 Refs)

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2. REACTIVITY OF MITOMYCIN C WITH SYNTHETIC POLYRIBONUCLEOTIDES CONTAINING GUANINE OR GUANINE ANALOGS.

Weaver J, Tomasz M
Dept. Chemistry, New York Univ., New York, NY, 10003
Biochim Biophys Acta; 697(2):252-254 1982

The guanine residues in nucleic acids are believed to be the major covalent binding site of the antibiotic mitomycin C. To identify the specific functional group in guanine which reacts with mitomycin C, reactions were run between the antibiotic and poly(G) analogs in which guanine was blocked at the N-7 or O-6 position, or lacked the 2-amino group. Binding ratios were affected to a small extent in the two former cases, but binding was significantly decreased in the absence of the 2-amino group. These results indicate that the most likely binding site of mitomycin C in synthetic polyribonucleotides is the 2-amino group of guanine residues. (Author abstract) (26 Refs)

3. CLEAVAGE OF DNA BY BLEOMYCIN AND TALISOMYCIN. THE ROLE OF SUBSTRATE TOPOLOGY IN DETERMINING THEIR SITE/SEQUENCE CLEAVAGE SPECIFICITY (MEETING ABSTRACT).

Mirabelli CK, Cheng-Hsiung H, Crooke ST
Bristol-Baylor Laboratory, Department of Pharmacology, Baylor College of Medicine, Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:6 1982

The effects of changes in the topological conformation of DNA on the site/sequence specific breakage of DNA by the antitumor antibiotics bleomycin A2 (BLM) and the talisomycin A (TLM) have been investigated. In this study, the site/sequence specificities of breakage by these drugs were compared using isolated: (1) linear restriction fragments, (2) whole, linear (form III), or (3) covalently closed, superhelical (form I) pBR 322 DNA. The specificity of drug-produced breaks using these forms of DNA as substrates as determined by DNA sequencing analyses are summarized: (1) The sequence specificity of BLM on linear DNA differs from that of TLM. (2) The specificities of BLM and TLM cleavage of linear DNA differed from those observed when form I DNA was used as substrate. (3) Although some of the drug-induced sequence specific breaks which occurred in linear DNA were also observed in form I DNA, a number of non-sequence breaks occurred in form I DNA that were not observed in linear DNA incubated with drug. (4) The non-sequence specific cleavage sites peculiar to form I DNA were observed with both BLM and TLM. (5) Using form I DNA as substrate, as the number of breaks produced by either drug per molecule of DNA increased, the extent of cleavage at the sequence-specific sites increased relative to that at the non-sequence specific sites. These results indicate that the specificity of cleavage of DNA by these drugs is influenced in part by the topological conformation of the substrate and may have important implications with respect to the mechanism by which these drugs interact with cellular DNA. (no Refs)

4. DEFECTIVE REMOVAL OF DNA CROSS-LINKS IN A REPAIR-DEFICIENT MUTANT OF CHINESE HAMSTER CELLS.

Meyn RE, Jenkins SF, Thompson LH
Dept. Physics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(8):3106-3110 1982

To further understand the relationships between DNA damage, DNA repair, and cellular end points such as survival and mutation, the repair capacity of a DNA repair-deficient mutant (strain UV-20) of Chinese hamster ovary cells was characterized in response to DNA cross-linking agents. This mutant, previously shown to be hypersensitive to killing by both ultraviolet light and the cross-linking agent mitomycin C, was also found to be extremely sensitive to cis-diamminedichloroplatinum, another DNA cross-linking agent. The efficiency of DNA cross-link removal after treatment with mitomycin C or cis-diamminedichloroplatinum was measured using the technique of alkaline elution and compared in wild-type Chinese hamster ovary cells and strain UV-20. Wild-type cells removed 80 or 95% of the cross-links within 24 hr after treatment with cis-diamminedichloroplatinum or mitomycin C, respectively. In contrast, UV-20 cells, which were equally as susceptible to cross-link damage as were wild-type cells, removed only a small proportion of the cross-links made by either agent. These results emphasize the importance of DNA repair processes in modulating the cytotoxic effects of chemicals that produce DNA cross-link damage and suggest that cross-link repair in chinese hamster ovary cells is controlled by a pathway that also repairs damage from ultraviolet radiation. (Author abstract) (26 Refs)

5. INTERSTRAND CROSSLINKS IN POLYDEOXYGUANOSINE: POLYDEOXYCYTOSINE (DG.DC) INDUCED BY CISPLATIN (MEETING ABSTRACT).

Lee CC, Harder HC
Department of Pharmacology, Oral Roberts University School of Medicine, Tulsa, OK, 74171
Proc Am Assoc Cancer Res; 23:19 1982

Cisplatin has been shown to create interstrand crosslinks in DNA by several methods. The purpose of this study was to determine if cisplatin coordinates crosslinks between guanosine and cytosine. Poly dG.dC was incubated with cisplatin at Pt/nucleotide ratios (ri) of 0.025 to 0.20 in 2 mM NaCl, 2 mM MOPS, pH 7.2 for 3 days at 20 C and then centrifuged in pH 12.9 cesium sulfate at 35,000 RPM for 64 hr. Untreated dG.dC resulted in a lower density dC and a higher density dG peak. Treated dG.dC yielded a density gradient having a hybrid-density third peak whose area was dose dependent while the area of the dC and dG peaks were inversely proportional to dose. With increasing ri the densities of both the dG and hybrid (crosslinked) peaks increased while that of the dC peak remained unchanged. Therefore, cisplatin reacts first with the dG strand followed by a second reaction with the dC strand to form the crosslink. Cisplatin added to dG.dC immediately after alkaline denaturation increased the density of the dG peak but did not yield a hybrid peak. Similar results occur after dG.dC incubation with monofunctional (diethylenetriaminechloroplatinum chloride) Cl. Hence cisplatin coordinates crosslinks between guanine and cytosine. However, due to the great distance between the N-7 of guanine and nearest binding site on a base in the opposite strand, it is highly improbable that such crosslinks can form after reacting first with the N-7 of guanine. (no Refs)

6. ALKYLATION OF GUANINE BY N-PROPYLDIAZONIUM ION. MOLECULARITY IS A FUNCTION OF BOTH NUCLEOPHILE AND ELECTROPHILE (MEETING ABSTRACT).

Scribner JD, Ford GP
Pacific Northwest Research Foundation, Seattle, WA, 98104
Proc Am Assoc Cancer Res; 23:235 1982

It has been reported that n-propyldiazonium ion alkylates N-7 of guanine in rat liver DNA to give 7-n-propylguanine, evidence that this ion reacts bimolecularly, without the formation of carbonium ions. It appeared to us, however, that N-7 of guanine may act as a highly nucleophilic trapping agent, and that weaker nucleophiles, such as O6, would react only with the less selective free carbonium ion. This was tested in vitro and in vivo, and theoretical studies undertaken to explain the results. Treatment of guanosine in water with n-propylnitrosourea gave a 3:1 ratio of O6/7 alkylation products. The only detectable O6 adduct was O(6)-isopropylguanosine, while the only detectable N-7 adduct was 7-n-propylguanosine. (3H)-Di-n-propylnitrosamine was injected into rats, which were sacrificed 12 hr later, and the liver DNA and RNA isolated. Portions of the RNA were digested enzymatically or with 1N HCl. The enzyme digest contained standard adducts, which were reisolated by ethyl acetate extraction and thin layer chromatography. After rechromatography of the standards, the specific activity of O(6)-i-propylguanosine was 7x higher than that of O(6)-n-propylguanosine. The acid digest was chromatographed directly with standards on a high resolution ion-exchange column, with a result like that of Park, et al. Thus we have shown that, while N-7 traps the n-propyldiazonium ion in a bimolecular reaction, O6 reacts predominantly in a manner which permits prior decomposition and rearrangement of the alkyl group, ie, alkylation of O6 has the properties of a unimolecular reaction. (1 Ref)

7. IN VITRO COMPARISON OF THE CYTOTOXIC AND CYTOKINETIC EFFECTS OF ADRIAMYCIN (ADR) ACLACINOMYCIN (ACL) AND CARMINOMYCIN (CAR) (MEETING ABSTRACT).

Wheeler RH, Natale RB, Clauw D, Dhafir R
University of Michigan, Ann Arbor, MI, 48109
Proc Am Assoc Cancer Res; 23:680 1982

ADR has a wide spectrum of activity in human neoplasms. ACL and CAR are new anthracyclines in early human trials. We have used a Burkitt Lymphoma cell line (P3J) to compare the cytotoxic and cytokinetic effects of these agents. Cytotoxicity of the three agents is concentration x time dependent in a manner characteristic of non-phase specific agents. Cytokinetic effects were determined by flow cytometry and thymidine incorporation (TI) following a 1 hour exposure to concentrations producing an IC10 to IC100 with or without the addition of colchicine to assess delay in G1/S and G2/S progression. ADR produced G2/S accumulation and a dose dependent slowing of S phase transit. CAR produced G2/M accumulation with little S phase effect and no G1S block. ACL produced a G1/S block at all concentrations and marked slowing of S phase transit. At the IC50 CAR did not inhibit TI, ADR produced 25% inhibition and ACL 75% inhibition. These three anthracyclines produce different dose dependent cytokinetic effects which must be considered in combination drug protocol design. (no Refs)

8. DIFFERENCES IN CHLOROETHYLNITROSOUREA (CNU)-INDUCED DNA INTERSTRAND CROSSLINKING AMONG CELL LINES DERIVED FROM HUMAN MALIGNANT GLIOMAS (MEETING ABSTRACT).

Erickson LC, Sariban E, Zlotogorski C, Laurent G, Kohn K, Smith B, Kornblith P
National Cancer Institute and National Institute of Health, Bethesda, MD, 20025
Proc Am Assoc Cancer Res; 23:641 1982

We have examined cell lines isolated following surgical resection of malignant glioma tumors. The 10 cell lines had - previously been classified as 'responders' and 'non-responders' using an in vitro microcytotoxicity assay. Using the alkaline elution technique each cell line was examined in the blind for its ability to avert interstrand crosslinking 6 hours after exposure to 50 and 100 uM CNU. Five cell lines were found to contain little or no interstrand crosslinks after CNU exposure; all 5 lines had been identified as non-responders in the microcytotoxicity assay. Three cell lines were found to have the expected levels of crosslinking in cells lacking in DNA monoadduct repair ability; these three lines had been classified as responders in the microcytotoxicity assay. The remaining 2 cell lines exhibited crosslinking levels intermediate between the 2 previous groups; these 2 cell lines had been classified as borderline non-responders in the microcytotoxicity assay. DNA-protein crosslinking, an indirect measure of drug penetration and/or inactivation, showed no significant differences between the groups. Collectively these data indicate that in malignant glioma there may be a group of tumors which have a DNA repair defect that makes these tumors susceptible to nitrosourea treatment. (2 Refs)

9. 9-DEAZAADENOSINE, A NEW POTENT ANTITUMOR AGENT (MEETING ABSTRACT).

Chu MY, Landry LB, Klein RS, Lim MI, Bogden AE, Crabtree GW
Division of Biology, Roger Williams General Hospital, Brown University, Providence, RI, 02908
Proc Am Assoc Cancer Res; 23:867 1982

The growth inhibition of 9-deazaadenosine (9-DAA), against 9 human solid human tumor lines (HRT-18; mesothelioma, VAMT-1; EP Breast; HCT-8, melanoma, Tang; MW Breast; pancreatic carcinoma, DAN; lung carcinoma LX-1 and ovarian carcinoma) was evaluated. ID50 values ranged from 1-8.5 x 10-8M. Studies with pancreatic carcinoma, DAN, in ATS-mice showed that 9-DAA (0.5 mg/kg/day for 3 days) reduced tumor weight to 16% of controls. Some weight losses and/or deaths were noted. Host toxicity was reduced when p-nitrobenzyl-6-thioinosine (NBMPR) a nucleoside transport inhibitor, was used in combination with 9-DAA. In vitro studies with pancreatic carcinoma, DAN and ovarian carcinoma cells showed that 9-DAA (10-5M for 2 hr) caused 34 and 68% inhibition of [3H]-uridine incorporation into RNA and DNA, respectively, and inhibited [3H]-thymidine incorporation into DNA by 80%. In these studies, peak which appeared in the triphosphate region of nucleotide profiles (determined by anion-exchange high pressure liquid chromatography) was tentatively identified as 9-deazaATP. These studies demonstrate that (1) 9-DAA is a potent growth inhibitor of 9 types of human solid tumor cell lines in vitro and of pancreatic carcinoma, DAN in vivo, (2) host toxicity to 9-DAA can be reduced by pretreatment with NBMPR, (3) 9-DAA can be incorporated into the nucleotide pools of treated cells and (4) 9-DAA may exert its effects, in part, by inhibiting the synthesis of RNA and DNA. (no Refs)

10. IN VIVO EFFECTS OF SEVERAL ANTHRACYCLINES ON DNA INTEGRITY.

Londos-Gagliardi D, Aubel-Sadron G
Centre de Biophysique moleculaire, CNRS, 1A, avenue de la Recherche Scientifique, 45045 Orleans-Cedex, France
FEBS Lett; 142(1):17-22 1982

Daunorubicin and various derivatives were administered to mice bearing an Ehrlich ascites tumor. Undegraded DNA was separated from tumor cells with use of a technique based on the isopyknic centrifugation of the nuclei followed by a CsCl gradient. The sedimentation constant of the DNA was determined in an alkaline ultracentrifuge, before and after alkaline degradation, and subsequently the number of single strand breaks was calculated. (21 Refs)

11. THE MECHANISM OF ACTION OF FAGARONINE, A NOVEL TUMOR INHIBITOR (MEETING ABSTRACT).

Pezzuto JM, Honig GR, Antosiak SK, Farnsworth NR
University of Illinois at the Medical Center, Chicago, IL, 60612
Proc Am Assoc Cancer Res; 23:812 1982

Fagaronine (2-hydroxy-3,8,9-trimethoxy-5-methyl benzo[c]phenanthridine) is an active antileukemic agent orginally isolated in our laboratory from the roots of Fagara zanthoxyloides. The present studies are concerned with its mechanism of action. Upon admixture with DNA, a significant hypochromic shift was noted in the absorption spectrum of fagaronine with a maximum at 395 nm. The magnitude of the shift was dependent upon the concentration of DNA, and clear isosbestic points suggest intercalative binding. Similar spectra were obtained with poly(dA-dT): poly(dA-dT) or poly(dG): poly(dC) indicating the interaction of fagaronine with these species, and this was confirmed by experiments involving gel filtration column chromatography. Fagaronine can also bind to ribonucleic acids containing double-stranded regions such as tRNA, poly(A): poly(U), poly(G): poly(C), and poly(I): poly (C), but isosbestic points were not discernable. Conversely, poly(A), poly(U), poly(G), poly(C), poly(I), AMP, UMP (uridine monophosphate), GMP (guanosine monophosphate), or CMP (cytidine monophosphate) can not effectively interact with fagaronine as judged by the absorption spectra. Additionally, the mutagenic potential of fagaronine was examined utilizing Salmonella typhimurium strain TM677. Fagaronine is not mutagenic. It is bactericidal, however, and this activity is greatly enhanced upon addition of a liver homogenate derived from Aroclor 1254 pretreated rats, and NADPH. N-Demethylfagaronine, a potential metabolite, is also not mutagenic. Moreover, it is not bactericidal and the addition of DNA does not significantly alter the absorption spectra. The results suggest that fagaronine functions by virtue of interaction with double-stranded nucleic acids, and the guanidinium functionality is required for binding. The active antitumor principle is probably a metabolite of fagaronine, and the chemical nature of this species is currently under investigation. (no Refs)

12. STUDIES ON THE MECHANISM OF ACTION OF THE NEW ONCOLYTIC THIAZOLE NUCLEOSIDE, 2-BETA-D-RIBOFURANOSYLTHIAZOLE-4-CARBOXAMIDE (NSC 286193) (MEETING ABSTRACT).

Jayaram HN, Cooney DA, Dion RL, Glazer RI, Ardalan B, Robins RK, Johns DG
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:856 1982

TR (2-beta-D-Ribofuranosylthiazole-4-carboxamide), a novel C-nucleoside, exhibits notable cytotoxicity against a variety of murine and human tumor cells in culture. Mechanism-of-action studies in P388 leukemia now reveal that the drug arrests cells in S phase, and inhibits the incorporation of tritiated thymidine, deoxycytidine and deoxyadenosine into nucleic acids; conversely the utilization of guanosine and deoxyguanosine is stimulated. Of the nucleic acid constituents examined, members of the guanosine family were unique in counteracting the inhibition of thymidine incorporation provoked by the drug. Guanosine also prevented the cytotoxicity of TR to Lewis Lung cells in culture. High pressure liquid chromatography analysis of PCA extracts of cultured cells confirmed that TR (10 uM) contracted the guanine nucleotide pools sharply and protractedly. Administration of [14C]HX to cells pretreated with TR (10 uM) revealed that little label reached C-nucleotides whereas there was a large accumulation of [14C] inosine monophosphate (IMP). Of the two enzymes unique to the biosynthesis of GMP, only IMP dehydrogenase (IMPD) was inhibited in extracts of treated cultures. Dialysis reversed such inhibition. In vivo after a single IP dose of 250 mg/kg of TR, maximum inhibition of IMPD was not reached until 30 minutes, with 50% restitution by 8 h and total restitution by 24 h. Curtailment of DNA synthesis and contraction of the guanosine triphosphate (GTP) and dGTP pools followed similar temporal patterns. In conclusion, these studies suggest that TR converted to an anabolite which in turn produces a state of guanine deprivation and thus restricts nucleic acid biosynthesis and cellular proliferation. (no Refs)

13. CELL CYCLE EFFECTS OF CC-1065 (MEETING ABSTRACT).

Bhuyan BK, Crampton SL, Adams EG
The Upjohn Company, Kalamazoo, MI, 49001
Proc Am Assoc Cancer Res; 23:802 1982

CC-1065 is a very potent antitumor agent which is lethal to B16 and CHO cells and to a variety of human tumors in clonogenic assay at less than 1 ng/ml. It is effective against L1210 leukemia and B16 melanoma at 1-50 ug/kg. CC-1065 binds to DNA in a non-intercalative manner in the minor groove. We report here the kinetics of inhibition of DNA synthesis and the cell-cycle effects of the drug. DNA synthesis was measured as H3-TdR (thymidine) incorporation into DNA at different times after 2-hr exposure to 1 or 5 ng/ml of CC-1065. At 1 ng/ml, % inhibition immediately after (0 hr) drug exposure, 4 hr, 19 hr, and 24 hr was 34, 10, 82, and 64% respectively. Similarly at 5 ng/ml, the % inhibition was minimum at 4 hr and maximum at 19 hr after drug exposure. Since cell progression studies showed a marked change in % S phase cells during this time, the DNA synthesis rate was recalculated at cpm/S phase cell. These results showed that % inhibition of DNA synthesis was minimum at 0 hr and gradually increased to maximum inhibition at 19 hr. Cell progression studies showed that 2-hr exposure to CC-1065 blocked cells predominantly in G2+M. At 5 ng/ml, cells also accumulated in S whereas at 1 ng/ml cells were temporarily slowed in S. This resulted in marked difference in phase distributions between cultures exposed to 1 or 5 ng/ml. To determine phase-specific toxicity, we started synchronous cultures either from mitotic cells (selectively harvested after colcemid block) or from elutriated phase fractions. The former cultures showed that cells in M were much more sensitive than cells in late G1/early S. However, cells in different phases obtained by elutriation seemed to be equally sensitive in all phases of the cell cycles. (1 Ref)

14. ON THE MECHANISM OF INTERACTION OF CC-1065 WITH DNA (MEETING ABSTRACT).

Swenson DH, Krueger WC, Petzold GL, Wallace TL, Li LH
The Upjohn Compnay, Kalamazoo, MI, 49001
Proc Am Assoc Cancer Res; 23:772 1982

The potent antitumor antibiotic, CC-1065, binds strongly to double-stranded DNA specifically at AT (adenine-thymine)-rich sites. To shed light on the mechanism of this specificity, the interaction between CC-1065 and a series of double-stranded polynucleotides was determined by circular dichroism and UV detection of Sephadex chromatographic eluates. The binding occurred primarily with polynucleotides in which the 0-2 position of the pyrimidine was free. At saturation levels, the CC-1065:DNA binding ratio ranged from 0.048 to 0.088 for the following polymers: poly(dA-I5dU), poly(dA-Br5dU), poly rA:poly dT, poly (dA-dT), poly dA:poly dT, poly(dI-dC), and poly dI:poly dC. Polynucleotide hybrids which contained even one strand of pyrimidine ribonucleotides showed reduced binding to CC-1065, presumably due to hydrogen bonding of the 2'-hydroxyl of the ribose moiety with the 0-2 of the pyrimidine. Thus, the binding ratios for poly rI:poly rC, poly rA:poly rU, poly dA:poly rU, and the triple-stranded poly rA:poly rU:poly rU were between 0 and 0.026. Poly(dG-dC) and poly dG:polydC, in which the O-2 of the pyrimidine is involved in base pairing, showed little or no binding. These data suggest that the main reason for selectivity of CC-1065 for minor groove AT sites is hydrogen bonding between the 0-2 of the thymidine residue and the drug. The binding of CC-1065 to DNA may be a cooperative process whereby the interaction of one drug molecule facilitates the binding of another nearby, since the thermal melting profile of poly(dA-dT) indicated a clustering of CC-1065 on the polynucleotide. (1 Ref)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

15. THE ANTICANCER AGENT ADRIAMYCIN CAN BE ACTIVELY CYTOTOXIC WITHOUT ENTERING CELLS.

Tritton TR, Yee G
Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Science; 217(4556):248-250 1982

The antineoplastic agent adriamycin was coupled to an insoluble agarose support. This material was actively cytotoxic to L1210 cells in culture under conditions in which no free adriamycin could enter the cell. It is concluded that an agent whose principal target was previously thought to be DNA can exert its cytotoxic action solely by interaction at the cell surface. (Author abstract) (16 Refs)

16. OVERVIEW OF RECENT DEVELOPMENT OF AROMATASE INHIBITORS.

Brodie AM
Dept. Pharmacology and Experimental Therapeutics, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201
Cancer Res; 42(8,Suppl):3312s-3314s 1982

Since the first publication in 1973 concerning aromatase inhibitors, several effective compounds have been reported by a number of investigators. Our studies with 4-hydroxyandrostene-3,17-dione, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstatrienedione indicate that these compounds cause rapid competitive inhibition of the enzyme. Aminoglutethimide binds competitively to cytochrome P-450 and inhibits a number of steroid hydroxylations but is more active as an aromatase inhibitor. 16alpha-Bromoandrogens and 7alpha-(4'-amino)phenylthioandrostenedione are also reported to be aromatase inhibitors. As yet, only some of these compounds have been evaluated in vivo, but all appear to be similarly effective in inhibiting aromatization in breast tumors in vitro. Recent interest has focused on enzyme inactivators or 'suicide' inhibitors. Such compounds act as substrates for the enzyme but are converted by the normal catalytic mechanism of the enzyme to reactive intermediates. These then bind covalently to the active site of the enzyme causing loss of activity. Active site-directed inhibitors are usually quite specific and have long-lasting effects in vivo. A number of new compounds, as well as some of the above compounds, appear to be inactivators of aromatase and are potentially interesting as agents for hormone-dependent breast cancer therapy. (Author abstract) (42 Refs)

17. A NEW HYPOTHESIS BASED ON SUICIDE SUBSTRATE INHIBITOR STUDIES FOR THE MECHANISM OF ACTION OF AROMATASE.

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Dept. Pharmacology, Washington Univ. Sch. Medicine, St Louis, MO, 63110
Cancer Res; 42(8,Suppl):3327s-3333s 1982

Recently, it was discovered that 4-hydroxy-4-androstene-3,17-dione, 4-androstene-3,17-trione, and 1,4,6-androstatriene-3,17-dione, compounds previously reported to be competitive inhibitors of aromatase, cause a time-dependent loss of aromatase activity in human placental microsomes. We report here that 1,4-androstadiene-3,17-dione (Ki 0.32 uM; Kinact 0.91 x 10(-3)/sec) and testolactone (Ki 35 uM; Kinact 0.36 x 10(-3)/sec) also cause a similar loss of aromatase activity. The mechanism which explains the unexpected loss of activity caused by these five inhibitors is neither established nor apparent from current theories of the enzyme mechanism of action of aromatase. We propose an inactivation mechanism based on a new hypothesis for estrogen biosynthesis in which the third enzyme oxidation carried out by aromatase results in the formation of an enzyme-bound intermediate. This intermediate is released as an aromatized product via a facile elimination reaction which simultaneously regenerates the unaltered active enzyme. Various structural modifications made in these five inhibitors are hypothesized to redirect this elimination reaction so that the steroid intermediate remains covalently attached to the enzyme instead of being released as an aromatized product. (Author abstract) (24 Refs)

18. COMPARATIVE STUDIES OF AROMATASE INHIBITORS IN CULTURED HUMAN BREAST CANCER CELLS.

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Dept. Internal Medicine, Veterans Admin. Medical Center, Iowa City, IA, 52240
Cancer Res; 42(8,Suppl):3378s-3381s 1982

The presence of aromatase activity, estrogen receptors, and estrogenic responsiveness in MCF-7 human breast cancer cells has allowed this cell line to be used as a unique in vitro system for investigating the biological activities of potentially therapeutic aromatase inhibitors. We now report the results of studies which have examined the cytotoxicity, antiaromatase, and intrinsic estrogenic activities of aminoglutethimide, 1,2-dehydrotestolactone (testolactone), dihydrotestosterone, 4-hydroxy-

4-androstene-3,17-dione, and 10-propargylestr-4-ene-3,17-dione within MCF-7 monolayer cultures. Cell viability was determined by trypan blue exclusion, and aromatase activity was assessed by quantifying the amounts of [3H]estradiol formed from [3H]testosterone. Estrogenic activity was assessed by examining the ability of each inhibitor to increase cytoplasmic progesterone receptor and deplete cytoplasmic estrogen receptor concentrations in these cells during a 5-day incubation period. Cytoplasmic progesterone and estrogen receptors were measured by the single-saturating-dose technique using [17alpha-methyl-3H]-17alpha,21-dimethyl-19-norpregna 4,9-diene-3,20-dione and [3H]estradiol as the labeled ligands for each assay, respectively. The results showed that all of these compounds were noncytotoxic aromatase inhibitors in MCF-7 cells but that these agents demonstrated marked differences in inhibitory potency (10-propargylestr-4-ene-3,17-dione greater than 4-hydroxy-4-androstene-3,17-dione much greater than dihydrotestosterone much greater than testolactone = aminoglutethimide). The incubation of cells with 4-hydroxy-4-androstene-3,17-dione resulted in cytoplasmic progesterone and estrogen receptor responses that were similar in magnitude to those observed in other cultures incubated with equimolar concentrations of estradiol. None of the other four agents demonstrated estrogenic activity in this system. However, we have previously observed that dihydrotestosterone has substantial antiestrogenic action in this system. Taken together, these results indicate that some aromatase inhibitors may influence the hormonal regulation of human breast cancer cells by more than one mechanism. (Author abstract) (12 Refs)

19. EFFECT OF AN AROMATASE INHIBITOR, 1,4,6-ANDROSTATRIENE-3,17-DIONE, ON 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED MAMMARY TUMORS IN THE RAT AND ITS MECHANISM OF ACTION IN VIVO.

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Biochem Pharmacol; 31(11):2017-2023 1982

In this study, 1,4,6-androstatriene-3,17-dione (ATD) was demonstrated to cause time-dependent loss of aromatase activity in rat ovarian microsomes in vitro. In vivo, an injection of ATD caused inhibition of ovarian aromatase and reduced estrogen secretion in pregnant mare's serum gonadotropin-primed rats for at least 24 hr after injection. In rats with 7,12-dimethylbenz[a]anthracene-induced, hormone-dependent, mammary tumors, marked regression occurred with ATD treatment. Although estrogen secretion was not reduced below the diestrus level of controls, the rats remained anestrus, indicating that the proestrus surge of estrogen was prevented. LH, FSH and prolactin levels were also basal and LH and FSH did not rise after ovariectomy. ATD had no detectable hormonal activity in bioassay. Consistent with this, the compound did not interact appreciably with either androgen or estrogen receptors, was not uterotrophic, and did not interfere with mammary tumor regression in ovariectomized rats. Thus, the major activities of the compound which cause mammary regression in the rat appear to be inhibition of estrogen synthesis, via aromatase and gonadotropin suppression. (Author abstract) (24 Refs)

20. DIMETHYLSULFOXIDE-INDUCED ALTERATIONS IN THE GROWTH PROPERTIES AND PROTEIN COMPOSITION OF IN VITRO-PROPAGATED MURINE HEPATOMA CELLS.

Higgins PJ, O'Donnell PV
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Oncology; 39(5):325-330 1982

The effects of the differentiation-inducing agent dimethylsulfoxide (DMSO) on the growth properties and protein synthetic capacity of BW77-1 mouse hepatoma cells were compared at various media concentrations of the polar solvent. DMSO produced a dose-dependent reduction in final population density, reduced or eliminated cell piling and stimulated synthesis of albumin. The rising albumin content reflected dose-related DMSO-induced increases in total cellular protein and in the albumin contribution to total cellular protein. In order to determine whether viral gene expression was associated with DMSO-induced stimulation of albumin synthesis, BW77-1 cultures were examined for the production of ecotropic and xenotropic Type C virus. The BW77-1 hepatic tumor cell line was determined to be a nonproducer of Type C virus by assays designed to measure extracellular reverse transcriptase, viral env gene product and infectivity on mouse and mink indicator cells. Type C virus could not be induced in BW77-1 cultures by treatment with DMSO under conditions which lead to a reduced proliferative capacity and enhanced expression of liver-specific genes. (Author abstract) (25 Refs)

21. VITAMIN B6 KILLS HEPATOMA CELLS IN CULTURE.

DiSorbo DM, Litwack G
Oncology Res. Lab., Nassau Hosp., Mineola, NY, 11501

Nutr Cancer; 3(4):216-222 1982

Data are presented which indicate that vitamin B6 (pyridoxine) can retard and eventually kill Fu5-5 rat hepatoma cells in culture. Additional studies indicate that the human kidney cell line 293-31, and a rat glial cell strain, C6, display growth characteristics similar to those of hepatoma cells when cultured in 5 mM pyridoxine-supplemented medium. However, the pyridoxine-supplemented culture medium had little effect on the growth of the human mammary cancer cell line MCF-7. The resistance of the MCF-7 cells to growth inhibition by vitamin B6 suggests that the vitamer pyridoxine must be metabolized to pyridoxal before it can act as a growth inhibitor. These findings suggest the potential use of vitamin B6 as an antineoplastic agent. Possible mechanisms by which vitamin B6 promotes this effect are presented. (Author abstract) (35 Refs)

22. EFFECTS OF RETINOIC ACID TREATMENT ON THE HL-60 HUMAN MYELOID LEUKEMIA CELL LINE (MEETING ABSTRACT).

Brewer G, Hnilica LS, Bloch D, McArthur B, Briggs RC
Department of Biochemistry, Vanderbilt University, School of Medicine, Nashville, TN, 37232

Proc Am Assoc Cancer Res; 23:37 1982

The induction of the promyelocytic leukemia cell line HL-60 to express more mature cell characteristics has been achieved by others using a number of different agents. Retinoic acid (RA) was discovered to be one of the most effective inducers of myeloid cell differentiation in the HL-60 cells. In the presence of 4 uM RA, the HL-60 cells changed in appearance from promyelocytes to metamyelocytes and later stage cells. The ability to induce oxidative metabolism (measured by nitroblue tetrazolium dye reduction assay) progressively increased from less than 5% of the cells in the untreated cultures to greater than 90% in the cultures with RA present. Daily cell counts showed a reduction in number after the third day of treatment. On the fifth day of treatment the number of viable cells was usually less than half that of the control. After three days of exposure to RA, flow cytometric analysis of DNA in the treated and control cultures revealed a reduction in the relative number of cells containing the S phase amounts of DNA in the treated cultures and an increased number of cells containing the G1 and G2+M DNA amounts. In conjunction with these studies, antisera were raised to human chromatin preparations including those from control and RA treated HL-60 cells and used to follow nonhistone protein changes during the induction process. The antigenic nonhistone proteins were detected after chromatin proteins were electrophoretically separated and transferred to sheets of nitrocellulose. The relationship of shifts in antigens present to the process of differentiation is being addressed. (no Refs)

23. POSSIBLE MECHANISM OF ACTION OF 2-BETA-D-RIBOFURANOSYL THIAZOLE-4-CARBOXAMIDE IN CHINESE HAMSTER OVARY CELLS (MEETING ABSTRACT).

Kuttan R, Lai M, Saunders PP
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Proc Am Assoc Cancer Res; 23:859 1982

NSC 286193, R090 (2-beta-D-Ribofuranosyl Thiazole-4-Carboxamide) is a recently synthesized compound with potential chemotherapeutic activity. We have attempted to find out the possible mode of action of this compound in Chinese Hamster Ovary Cells (CHO-cells). R090 is toxic to CHO-cells at 1-5 um. Incorporation of 14C-formate into guanylate was markedly inhibited by R090 (10 um) without showing a similar effect on adenylate synthesis suggesting a correlation between R090 toxicity and guanylate metabolism. Addition of R090 to CHO-cells severely inhibited IMP (inosine monophosphate) dehydrogenase activity. R090 was phosphorylated to its 5'-monophosphate which was found to be a weak non-competitive inhibitor of inosine monophosphate (IMP)-dehydrogenase. R090-Monophosphate was found to be converted to another compound, in vivo and in vitro, which is a strong non-competitive inhibitor of IMP dehydrogenase. Nucleotide pyrophosphatase cleaved this compound to R090-Monophosphate and AMP; hence this compound is presumably R090-Adenine dinucleotide. As an added proof it was found that when a cell sonicate was incubated with R090-Monophosphate and 2-3H-ATP, radioactivity from ATP was incorporated into this inhibitor. R090-resistant cell lines synthesize R090-Monophosphate but appear unable to synthesize this inhibitor. (no Refs)

24. ANTITUMOR AGENTS LII: THE EFFECTS OF MOLEPHANTININ ON NUCLEIC ACID AND PROTEIN SYNTHESIS OF EHRLICH ASCITES CELLS.

Hall IH, Liou YF, Lee KH
Div. Medicinal Chemistry, Sch. Pharmacy, Univ. North Carolina, Chapel Hill, NC, 27514
J Pharm Sci; 71(6):687-690 1982

Molephantinin, a germacranolide, has previously been shown to possess antineoplastic activity in rodents. The principle effect of molephantinin on Ehrlich ascites carcinoma cells was to depress DNA and protein synthesis both in vivo and in vitro. DNA synthesis was inhibited at the following sites: DNA polymerase, purine synthesis specifically at inosinic acid dehydrogenase and to a lesser degree at dihydrofolate reductase, pyrimidine synthesis at orotidine monophosphate decarboxylase, thymidine kinase, histone phosphorylation, and oxidative phosphorylation processes. The protein synthesis inhibition pattern resembled more an initiation inhibitor as opposed to an elongation inhibitor. (Author abstract) (32 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

25. OXYGEN TENSION, CELLULAR RESPIRATION, AND REDOX STATE AS VARIABLES INFLUENCING THE CYTOTOXICITY OF THE RADIOSENSITIZER MISONIDAZOLE.

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Radiat Res; 91(1):104-123 1982

The O2 dependence for the cytotoxicity of misonidazole (MIS) was measured using Chinese hamster ovary cells and Chinese hamster lung fibroblasts CCL16-B1 and a respiration-deficient (res-) mutant derived from this line. MIS did not significantly affect O2 utilization rates in intact cells, and hence did not alter initial O2 equilibrium values. MIS caused time-dependent changes in cellular O2 utilization rates, which resulted in increased O2 measured in sol. and a sparing effect on remaining viable cells. Changes in O2 utilization rates apparently do not occur in the absence of appreciable toxicity. Having an inherent block in respiration (res- mutant) did not alter sensitivity to cytotoxic effects of MIS under anoxic conditions, indicating that the toxic effects of MIS on respiration do not appear to play a causal role in toxicity. O2 levels less than 200 ppm produced a 50% reduction in the rate of cell killing. At very low levels diffusion problems raise questions about the exact O2 available in the cell. KCN altered both the aerobic toxicity and the hypoxic cell toxicity of MIS; there is evidence for an electron transport relationship in the latter effect. In contrast, the effects of KCN on the aerobic toxicity of MIS may be completely independent of its inhibitory effect on electron transport enzymes (cytochrome oxidase), since KCN modified the sensitivity of res- mutant and parental cell equally. Calculations showed that O2 levels in vivo must be very low for appreciable toxicity to occur with MIS, but the KCN effects suggest that other factors may also determine degree of reductive drug metabolism and toxicity. (35 Refs)

26. INTERACTION OF METHOTREXATE POLY(L-LYSINE) WITH TRANSFORMED HEPATIC CELLS IN CULTURE.

Galivan J, Balinska M, Whiteley JM
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Arch Biochem Biophys; 216(2):544-550 1982

Role of poly(L-lysine) as a carrier for methotrexate (MTX) was studied in H35 hepatoma cells and their transport-resistant counterparts, H35R0.3 cells. H35 andH35R0.3 cells were equally susceptible to MTX poly(L-lysine), but an 86-fold difference in the sensitivity to MTX was observed, which was reflected in the reduced uptake of MTX by the resistant subline. Both cell types accumulated much more MTX linked to poly(L-lysine) than MTX alone. MTX poly(D-lysine) was accumulated by both cell types to the same extent as the L-conjugate.

MTX poly(L-lysine) completely inhibited cell growth at 200 nanoM, whereas a comparable concentration of poly(L-lysine) alone caused only a modest (less than 10%) inhibition of cell growth. MTX poly(L-lysine) exhibited extensive hydrolysis in H35 and H35R0.3 cells. Uptake of MTX by H35 cells was severely depressed in the presence of folinic acid. In contrast, inclusion of folinic acid during [3H]MTX poly(L-lysine) uptake had no effect on cellular accumulation of the unbound MTX pool demonstrating that cellular entry of the complex proceeds the liberation of MTX. Results demonstrated that MTX poly(L-lysine) enters the cells as an intact complex independent of the MTX and reduced folate coenzyme transport system. MTX poly(L-lysine) is then hydrolyzed yielding MTX by a lysosomal mechanism. The liberated MTX or its polyglutamate forms are then free to bind to the target site, dihydrofolate reductase, resulting in a blockage of folate coenzyme function. (21 Refs)

27. DIETARY INFLUENCE OF TYROSINE AND PHENYLALANINE ON THE RESPONSE OF B16 MELANOMA TO CARBIDOPA-LEVODOPA METHYL ESTER CHEMOTHERAPY.

Meadows GG, Pierson HF, Abdallah RM, Desai PR
Coll. Pharmacy, Washington State Univ., Pullman, WA, 99164
Cancer Res; 42(8):3056-3063 1982

The effect of dietary tyrosine and phenylalanine on survival of adult female C57BL/6 x DBA/2 F1 mice bearing ip slow-growing, moderately pigmented and fast-growing, highly pigmented B16 melanoma tumors was studied alone and in combination with carbidopa-levodopa methyl ester chemotherapy. These studies tested three different diets: a natural product diet containing 1.09% phenylalanine and 0.64% tyrosine (commercial diet); a chemically defined crystalline amino acid diet containing 0.6% phenylalanine and 0.3% tyrosine (purified diet); and a nutritionally deficient chemically defined diet containing 0.08% phenylalanine and 0.04% tyrosine (deficient diet). Mice received carbidopa (100 mg/kg) and levodopa methyl ester (1,000 mg/kg) ip daily for 12 days. The median survival of mice bearing the slow-growing tumor averaged 8 days longer than that of mice bearing the fast-growing tumor. Median survival increased by 42% (slow-growing tumor) and by 30% (fast-growing tumor) in mice maintained on the deficient diet. Drug treatment significantly increased survival in mice maintained on the purified and deficient diets but was relatively ineffective in mice maintained on the commercial diet regardless of the tumor growth characteristics. The largest increases in median survival of 61% (slow-growing tumor) and of 78% (fast-growing tumor) occurred in the treated mice maintained on the deficient diet. Plasma tyrosine and phenylalanine levels decreased by 33 and 21%, respectively, in mice maintained on the deficient diet and were unaffected by drug treatment. Tumors were 60% smaller in mice maintained on the deficient diet compared to mice maintained on the purified diet. Drug treatment resulted in decreased food intake and wt loss in all tumor-bearing dietary groups. Restricting food intake in untreated tumor-bearing mice to the amounts consumed by the drug treatment groups resulted in a parallel loss in body wt but no significant alteration in median survival. These data show that concomitant dietary tyrosine-phenylalanine restriction enhances the antitumor activity of carbidopa-levodopa methyl ester against B16 melanoma. (Author abstract) (51 Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

28. ANALYSIS OF ACTIVITIES FOR ALTERNATE ACTIVATION OF 5-FLUOROURACIL (FU) BY 1-PYROPHOSPHORIBOSYL-5-PHOSPHATE (PPRP) AND RIBOSE-1-PHOSPHATE (R-1-P) IN BONE MARROW AND TUMOR TISSUES (MEETING ABSTRACT).

Schwartz PM, Hyde CM, Komp DM, Handschumacher RE
Department of Pharmacology, Yale University, New Haven, CT, 06510
Proc Am Assoc Cancer Res; 23:780 1982

We measured the activities of enzymes that converted FU to 5-Fluorouridine monophosphate (FU + PPRP vs FU + R-1-P and FUR + ATP) as a determinant of differential activation of FU in bone marrow and tumor tissues. The activities (nmole/mg/hr) for FU + PPRP in bone marrow were: 22.8 for mouse, 12.5 for rat and 2.1 for human; and in tumors: 48.9 for RPMI rat colon tumor, 42.0 for L5178Y ascites and 28.1 for colon tumor number 38. Activities of the alternative pathway, FU + R-1-P leading to FUR, were 2-20 times greater (40-248 nmole/mg/hr) than that for FU + PPRP except in L5178Y ascites. In L5178Y cells (low sensitivity to FU), the ratio of activities of FU + PPRP: FU + R-1-P was 1:0.1, a result markedly different from the 1:5-8 ratio seen in the FU-responsive tumors (colon tumor number 38 and RPMI rat tumor). Unexpectedly, the ratio of activities for FU activation in normal marrow cells which are spared from FU toxicity by allopurinol (HPP) was similar to that measured in FU-sensitive tumors. FUR kinase activity was high in all rodent tissues and would not limit activation of FU via the R-1-P pathway. However, the balance of enzyme activities as well as the availability of the endogenous ribose donors (R-1-P and PPRP) would be the ultimate determinants of the differential activation of FU. (no Refs)

29. DOXORUBICIN (ADRIAMYCIN) TRANSPORT IN NUCLEATED AND NON-NUCLEATED CELLS SHOWS FEATURES OF A SIMPLE DIFFUSION TRANSPORT PROCESS (MEETING ABSTRACT).

Dalmark M, Hoffmann EK
Clinical Pharmacology Branch, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:14 1982

Previously published data indicated that doxorubicin (DOX) transport in human red cells is a simple Fickian diffusion transport process. The characteristics of DOX transport in the nucleated Ehrlich ascites tumor cells were investigated and compared with those of the non-nucleated human red cells. The Ehrlich ascites tumor cells (hyperdiploid strain) were maintained by weekly intraperitoneal transplantation in white female NMRI mice and harvested 8 days after transplantation. The apparent permeability coefficient in ascites cells and in red cells was of the same order of magnitude when calculated from the initial net uptake at 37 C and pH 7.3. DOX was strongly absorbed to the cell surface of ascites cells in contrast to the adsorption to red cells. The absorbed DOX was removed by washing the cells either with a DNA or a human albumin salt solution indicating the adsorption was reverisble to cell surface components in front of the rate limiting barrier. Cell membrane modifiers, 1-alcohols, local anesthetics, phloretin, HgCl2, parachloromercuribenzoate, affected DOX transport in ascites tumor cells and red cells in the same manner as these modifiers affected the transport of other lipophilic compounds. Ehrlich ascites tumor cells and human red blood cells appeared to represent two extremes with regard to DOX adsorption to cell surfaces but DOX transport through the rate limiting barrier of the cell membrane might be simple diffusion transport process of the uncharged DOX molecule in both cell types. (1 Ref)

30. CELLULAR PHARMACOKINETICS OF ACLACINOMYCIN A IN CULTURED L1210 CELLS: COMPARISON WITH DAUNORUBICIN AND DOXORUBICIN.

Zenebergh A, Baurain R, Trouet A
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Cancer Chemother Pharmacol; 8(2):243-249 1982

The cellular pharmacokinetics of aclacinomycin A (ACM), doxorubicin (DOX), and daunorubicin (DNR) in cultured L1210 cells were compared with the aid of cell fractionation techniques and drug determination by high pressure liquid chromatography and fluorometry. The uptake of ACM occurred at a greater speed than that of DNR or DOX, reaching a maximal drug concentration 30 min after incubation. In addition to the parent compound two fluorescent metabolites were separated. Uptake of DNR was biphasic, with an initial rapid phase followed by a slower one, while intracellular DOX levels increased steadily during the assay. ACM was released from cells to the highest extent, about 60% escaping within the first 2 hr. Metabolic inhibitors (iodoacetate or antimycin A) had no effect upon accumulation of ACM, but did affect the release of the drug. Inhibition of incorporation of tritiated thymidine into cellular DNA was more rapid and extensive with ACM than with DNR or DOX. DNR and DOX were associated with DNA and lysosomes while ACM was mainly localized in the nuclei. (26 Refs)

31. CLONAL VARIATION IN THE SENSITIVITY OF B16 MELANOMA TO M-AMSA.

Stephens TC, Peacock JH
Radiotherapy Res. Unit, Div. Radiotherapy, Inst. Cancer Res., Sutton, Surrey, England
Br J Cancer; 45(6):821-829 1982

A hypothesis that m-AMSA may have greater cytotoxicity in melanin-containing tumor tissues, because it may reversibly bind to melanin, leading to prolonged drug exposure, was examined. Clonal lines of B16 melanoma which differed widely in pigmentation level were selected by isolating artificial lung colonies and in vitro soft-agar colonies, and implanting them into mice. Excision cell-survival assays performed 24 hr after drug administration showed that in vivo sensitivity to m-AMSA progressively increased as pigmentation level decreased, but that m-AMSA drug levels measured 24 hr after treatment were much lower in amelanotic than in melanotic lines. In dose-survival studies the reduced sensitivity of melanotic cell lines was revealed as a large shoulder (Dq = 27 mg/kg) though the terminal slopes for melanotic and amelanotic cell lines were similar (D10-approx 31 mg/kg). Time-course studies indicated that there was no significant loss of drug from a melanotic cell line for 72 hr after drug administration, though in an amelanotic cell line drug levels fell 10-fold in 10 hr. There was, however, no evidence for prolonged drug cytotoxicity in the melanotic cell line. Using a fractionated drug-treatment regime, the greater cytotoxicity of m-AMSA to amelanotic tumor tissue was confirmed in a non-invasive regrowth-delay assay. (Author abstract) (15 Refs)

32. MECHANISM OF ACTION OF 5-FLUORODEOXYURIDINE IN HELA CELLS 'SELF POTENTIATION' (MEETING ABSTRACT).

Nakayama K, Cheng Y
Department of Pharmacology, University of North Carolina, Chapel Hill, NC, 27514
Proc Am Assoc Cancer Res; 23:844 1982

Exposure of HeLa cells to 10-7M 5-fluorodeoxyuridine (FUdR) caused inhbitition of cell growth which could be reversed by thymidine, but not by uridine. The intracellular deoxythymidine triphosphate pool rapidly decreased 30 min after exposure to the drug, and started to increase after 3 h. Fragmentation of pre-existing DNA was observed, and the newly synthesized DNA was found to be smaller in size compared with that of the untreated cells. Incorporation of Fluorodeoxyuridylate (FdUMP) into DNA was observed, and was dependent on the time of exposure and the concentration of the drug. The amount of FdUTP in cells appeared very low, which might be due to the presence of the high activity of dUTP pyrophosphatase. These observations support the following hypothesis on the mechanisms of the action of FUdR: FUdR is phosphorylated to FdUMP which inhibits thymidine monophosphate (TMP) synthetase, and results in decreased intracellular thymidine nucleotide pools. Phosphorylation of FdUMP to FdUTP and subsequent incorporation into DNA would be facilitated by the decreased thymidine nucleotide pool. The incorporated FU could be cleaved out of DNA by the action of uracil-DNA glycosylase, followed by a series of repair events which involve gap formation and filling. The process of gap formation might be responsible for the increased dTTP pool observed from 3 h after the exposure to the drug. Thus, FUdR potentiates its own DNA fragmentation action, which could result in cell death, through inhibition of thymidine nucleotide formation, its incorporation into DNA, and subsequent cleavage from DNA. (no Refs)

33. STUDIES ON THE BIOLOGIC ACTIVITY OF PURINE AND PYRIMIDINE ANALOGS.

Montgomery JA
Southern Res. Inst., Birmingham, AL, 35255
Med Res Rev; 2(3):271-308 1982

Biologic activity of purine-pyrimidine antimetabolites including 6-thiopurines, azapurine, alpha-arabinonucleotides, carbolic analogs of nucleosides, purines and pyrimidines containing chemically reactive functions, deazapurines, and halopurines is reviewed. Among 9-substituted purines, 9-amino-6-mercaptopurine and some of its derivatives showed activity in the L1210 system comparable to 6-mercaptopurine (MP) and may owe their activity to in vivo conversion to MP. The responses of resistant cell lines indicated that the cytotoxicity of 2-azaadenosine is due both to its direct phosphorylation and to its conversion to 2-azahypoxanthine which is known to inhibit the growth of both microbial and mammalian cells. Carbocyclic analogs of nucleosides have a carbon-nitrogen bond joining the heterocyclic base to the cyclopentane ring comparable to that of simple alkyl derivative and, therefore, not susceptible to enzymatic fission as is the glycosyl bond of true nucleosides. The activity of the monofunctional alkylating agent N-(2,4-dinitrophenyl)aziridine provided the basis for the synthesis of some 6-(1-aziridinyl)purines, which showed activity against adenocarcinoma 755, a tumor not normally sensitive to alkylating agents. The activity of N-methyl-N-nitrosourea suggested the incorporation of this moiety into a purine structure. The cytotoxicity of 3-deoxyadenosine is enhanced by 2'-deoxycoformycin, which is less effective with 9-beta-D-xylofuranosyladenine, even though both compounds are deaminated by adenosine deaminase at a significant rate. (175 Refs)

34. STUDIES ON THE O-DEMETHYLATION OF MISONIDAZOLE BY RAT LIVER MICROSOMES.

Shoemaker DD, McManus ME, Hoerauf R, Strong JM

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Cancer Treat Rep; 66(6):1343-1347 1982

The role of rat liver microsomes in the O-demethylation of misonidazole to desmethylmisonidazole was studied. The rate of the microsomal-dependent formation of desmethylmisonidazole was linear up to a protein concentration of 2 mg/ml and over a 10-min interval. The metabolism was optimal in a system comprised of microsomes, O2, and NADPH. Metabolism in incubation mixtures continuously flushed with N2 was inhibited by 78%. The O-demethylase activity was competitively inhibited by the addition of SKF 525-A, with a Ki of approx 1 x 10(-5) M. The Km and Vmax values of normal microsomes were 1.87 +-0.30 mM and 413 +-14 pmols/minute/mg of microsomal protein, respectively. Pretreatment of rats with phenobarbital for 7 days prior to preparation of the microsomes resulted in no significant change in the Km, but the Vmax was considerably increased to 1,033 +-203 pmols/minute/mg of microsomal protein. The results demonstrate that the O-demethylation of misonidazole is mediated by cytochrome P-450. (Author abstract) (16 Refs)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

35. DIAZOKETONE AND CHLOROMETHYLKETONE ANALOGS OF METHOTREXATE AS POTENTIAL ANTITUMOR AGENTS.

Gangjee A, Kalman TI, Bardos TJ

Dept. Pharmaceutical Chemistry and Pharmaceutics, Sch. Pharmacy, Duquesne Univ., Pittsburgh, PA, 15282

J Pharm Sci; 71(6):717-719 1982

The synthesis of 4-amino-4-deoxy-N10-methylpteroyl-(6-diazo-5-oxo)-L norleucine and 4-amino-4-deoxy-N10-methylpteroyl-(6-chloro-5-oxo)-L norleucine, analogs of methotrexate in which the gamma-carboxyl group is replaced by a diazoketone and a chloromethylketone, respectively, was carried out. The analogs inhibited the growth of leukemia L-1210 cells in culture by 50% at 4 x 10(-7) M and 2 x 10(-7) M, respectively and were effective inhibitors of the synthesis of thymidylate in L-1210 cells in vitro (I50 = 3 x 10(-6) M), exhibiting significant antifolate activity. The results demonstrated the feasibility of introducing chemically reactive groups at the gamma-position of pteroyl glutamates with retention of biological activity. However, in the systems investigated thus far, there was no evidence of covalent bond formation due to these reactive groups at the active sites of the enzymes. (Author abstract) (23 Refs)

EFFECTS OF ANTIMETASTATIC AGENTS

36. ROLE OF NK CELLS IN THE CONTROL OF METASTATIC SPREAD AND GROWTH OF TUMOR CELLS IN MICE.

Gorelik E, Wiltrout RH, Okumura K, Kabu S, Herberman RB
Lab. Immunodiagnosis, NCI, Bethesda, MD
Int J Cancer; 30(1):107-112 1982

The ability of BALB/c nude and C57BL/6 mice to eliminate tumor cells from the blood stream was severely impaired after a single inoculation of 0.2 ml of anti-asialo BMI (asGMI) serum, diluted 1:40 to 1:320. The number of iv-inoculated YAC-I cells surviving in the lungs of BALB/c nude mice pretreated with anti-asGMI serum was 28x higher than in the control nude mice. The increase in the initial survival of tumor cells that was induced by pre-treatment with anti-asGMI resulted in a substantial increase in the number of artificial lung metastases that developed. In C57BL/6 +/+ mice treated with anti-asGMI and in C57BL/6 beige mice, iv inoculation of B16 melanoma cells induced 10x more metastatic foci in the lungs than in the control C57BL/6 +/+ mice. In contrast, in nude mice which possess higher levels of NK reactivity, metastatic growth was suppressed seven-fold in comparison with intact C57BL/6 +/+ mice. Data indicate that B16 melanoma cells are able to grow in the liver, but their growth is ordinarily prevented by NK cells. The antimetastatic defense of C57BL/6 mice treated by anti-asGMI could be restored by transplantation of 40 x 10(6) normal spleen cells. This antimetastatic effect of transplanted spleen cells was mediated by asGMI-bearing cells since after in vitro pretreatment of normal spleen cells with anti-asGMI and complement, they lost their ability to inhibit the development of artificial metastases in the lungs of C57BL/6 mice. Suppression of NK reactivity by multiple injections of anti-asGMI in C57BL/6 mice inoculated intrafootpad with B16 melanoma or 3LL tumor cells, did not influence the growth of local tumors, but dramatically accelerated the development of spontaneous pulmonary metastases. These data demonstrate that NK cells may play an important role in resistance to the dissemination of tumor cells, and therefo[illegible]ontribute to the control of metastasis formation in mice. (21 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

37. N,N'-DIALKYL-1,2-BIS(HYDROXYPHENYL)ETHYLENEDIAMINES AND N,N'-DIALKYL-4,5-BIS(4-HYDROXYPHENYL)IMIDAZOLIDINES: SYNTHESES AND EVALUATION OF THEIR MAMMARY TUMOR INHIBITING ACTIVITY.

von Angerer E, Egginer G, Kranzfelder G, Bernhauer H, Schonenberger H

Institut fur Pharmazie der Universitat Regensburg, Universitatsstrasse 31, D-8400 Regensburg, W. Germany

J Med Chem; 25(7):832-837 1982

Diastereomeric N,N'-dialkyl-1,2-bis(hydroxyphenyl)ethylenediamines (5) were synthesized and tested for their affinity for the estradiol receptor. Only the (+-

)-1,2-bis(4-hydroxyphenyl)ethylenediamines with the alkyl groups C3H7 [(+-)-5c, Ka = 1.1 x 10(6)], C4H9 [(+-)-5e, Ka = 3.6 x 10(6)], and C5H11 [(+-)-5h, Ka = 2.2 x 10(6)] showed a marked affinity, which is mainly due to the (+) enantiomers [eg, (+)-5e, Ka = 2.1 x 10(7)]. No enhancement of affinity by cyclization to imidazolidines [eg, (+-)-trans-7a, Ka = 1.2 x 10(7)] was observed. These compounds [eg, (+-)-, (+)-, and (-)-5e], which did not produce any uterine response in the mouse, were able to inhibit weakly the growth of the DMBA-induced mammary carcinoma of the rat. The inhibitory effect of (+-)-5e against MCF-7 cells, which can be overcome by hexestrol, makes a direct antiestrogenic mode of action probable, since general cytotoxic effects and a central action could be ruled out. (Author abstract) (27 Refs)

38. ANTITUMOR EFFECT OF POLYSACCHARIDE TC-13 ON ALLOGENEIC AND SYNGENEIC TUMORS IN MICE.

Kohno M, Abe S, Yamazaki M, Mizuno D
Res. Inst., Dalich Seiyaku Co., Ltd., Kitakasai 1-16-13, Edogawa-ku, Tokyo 134, Japan
Gan; 73(3):488-494 1982

The antitumor activity of TC-13, a protein-bound polysaccharide extracted from a rare actinomycetes was tested on allogeneic and syngeneic tumors in mice. In the allogeneic Ehrlich carcinoma system, TC-13 showed antitumor activity over a broad optimal dose range, when administered by various routes such as ip, iv, sc, it (intratumorally) or po, even when given before tumor inoculation. TC-13 showed synergistic antitumor effects in combination with other immunomodulators, eg, lipopolysaccharide, lentinan and picibanil. It showed antitumor activity against syngeneic tumors, MM46 mammary carcinoma and MCS-8 and Meth A fibrosarcoma. (Author abstract) (22 Refs)

39. NEW INHIBITORS OF THE PYRIMIDINE NUCLEOSIDE PHOSPHORYLASES (MEETING ABSTRACT).

Niedzwicki JG, El Kouni MH, Chu SH, Cha S
Division of Biology and Medicine, Brown University, Providence, RI, 02912
Proc Am Assoc Cancer Res; 23:845 1982

Eighty pyrimidine base and nucleoside analogs were tested for inhibition of Sarcoma S-180 uridine phosphorylase (E.C. 2.4.2.3) and and partially purified mouse liver thymidine phosphorylase (E.C. 2.4.2.4). Two previously unrecognized inhibitors were identified. 2,6-Pyridinediol, which exists in solution as 1-deazauracil and the mono-keto tautomer thereof in a 1:4 molar ratio, inhibited uridine phosphorylase 57-fold better than uracil. 6-Benzyl-2-thiouracil inhibited thymidine phosphorylase, but not uridine phosphorylase, with a 5-fold enhancement of binding relative to uracil. Additionally, structure-activity relationships for the binding of pyrimidine analogs to the pyrimidine nucleoside phosphorylases became apparent. The 2-oxo group and N-3 proton but not the 4-oxo group of uracil analogs are apparently involved in hydrogen bonding to uridine phosphorylase. Attachment of certain hydrophobic groups to the 5-position enhances the binding of uracils to uridine phosphorylase presumably through interaction with the postulated 'hydrophobic pocket' on the enzyme. Electron withdrawing substituents (e g, fluoro-, bromo-, and nitro-) at the 5-position enhance the binding of uracils to both uridine phosphorylase and thymidine phosphorylase, possibly due to facilitated dissociation of the N-1 proton. (3 Refs)

INTERFERON AND OTHER ANTIVIRALS

40. INHIBITORY EFFECT OF E-5-(2-BROMOVINYL)-1-BETA-D-ARABINOFURANOSYLURACIL ON HERPES SIMPLEX VIRUS REPLICATION AND DNA SYNTHESIS.

Descamps J, Sehgal RK, De Clercq E, Allaudeen HS
Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Virol; 43(1):332-336 1982

The effect of E-5-(2-bromovinyl)-1-beta-D-arabinofuranosyluracil (BVaraU) on herpes simplex virus (HSV) replication was examined and compared with that of E-5-(2-bromovinyl)-2'-deoxyuridine (BVdUrd). The 50% inhibitory dose against HSV type 1 (HSV-1) was 0.1 ug/ml compared with 0.008 ug/ml for BVdUrd; the antimetabolic 50% inhibitory dose of BVaraU ranged from 20 to 95 ug/ml. The addition of 50 ug of BVaraU per ml to HSV-1-infected Vero cells decreased the synthesis of viral and cellular DNA by 37 and 28%, respectively. The 5'-triphosphate (BVaraUTP) competed with dTTP in DNA synthesis by the herpes-viral and cellular DNA polymerases; the apparent Ki values of HSV-1 DNA polymerase, DNA polymerase alpha, and DNA polymerase beta were 0.14, 0.32, and 5 uM, respectively. Thus, BVaraU was a less effective antiherpesvirus agent than BVdUrd; unlike BVdUrd, it did not appear to be internally incorporated into replicating DNA in virus-infected cells. (Author abstract) (13 Refs)

41. PERTURBATION OF THE SWITCH-ON OF TRANSCRIPTASE ACTIVITY IN INTERMEDIATE SUBVIRAL PARTICLES FROM REOVIRUS.

Borsa J, Sargent MD, Ewing DD, Einspenner M
Medical Biophysics Branch, Whiteshell Nuclear Res. Establishment, Atomic Energy Canada Res. Co., Pinawa, Manitoba ROE 1L0, Canada
J Cell Physiol; 112(1):10-18 1982

Studies on the effects of a varied group of agents to switch-on their endogenous transcriptase in reovirus intermediate subviral particles (ISVP) is presented. The study showed that many of the agents which affect cell differentiation in a variety of systems also have an effect on the switch-on process in reo ISVP, and suggests that these particles may be a useful model system for examining some aspects of the function of gene switches in cells. (39 Refs)

42. MECHANISM OF STIMULATION BY HUMAN INTERFERON OF PROSTAGLANDIN SYNTHESIS IN HUMAN CELL LINES.

Fuse A, Mahmud I, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
Cancer Res; 42(8):3209-3214 1982

Human interferon beta (IFN-beta) stimulated the synthesis of prostaglandin E (PGE) and prostaglandin F2alpha in IFN-sensitive RSa and GM258 cell lines, but not in IFN-resistant HEC-1 cells. IFN-beta at a concentration of 1,000 units/ml elicited two- to three-fold increases in PGE production in these cell lines. In the presence of exogenous arachidonic acid (1 ug/ml), IFN-pretreated cells produced five-fold more PGE compared to the cell cultures in the absence of arachidonic acid. Prednisolone, an inhibitor of phospholipase A2, at a concentration of 2 ug/ml inhibited the enhanced synthesis of PGE by IFN-pretreated cells. Indomethacin (4 ug/ml), a potent fatty acid cyclooxygenase inhibitor, also inhibited the increased synthesis of PGE. IFN stimulated the release of [14C]arachidonic acid from phospholipids but did not stimulate the activity of fatty acid cyclooxygenase. These data suggest that IFN stimulates prostaglandin synthesis by promoting the release of arachidonic acid from phospholipids. Since cycloheximide and actinomycin D inhibited the stimulation of PGE synthesis, the stimulation of prostaglandin synthesis by IFN seemed to be due to de novo enzyme synthesis, which catalyzes the release of fatty acid. Addition of exogenous PGE suppressed the growth of RSa and GM258 cells. Prednisolone and iodomethacin partially inhibited anti-cell growth activity of IFN, suggesting a possibility that IFN-inhibited cell growth was partly medirted by prostaglandins. (Author abstract) (55 Refs)

43. EFFECT OF INTERFERON-SS ON NATURAL KILLER CELLS: ANALYSIS OF THE MECHANISM OF ACTION (MEETING ABSTRACT).

Schmitz-Drager BJ, Hayakawa M, Ackermann R
Urologische Klinik und Poliklinik der Universitat Wurzburg, Wurzburg, W. Germany
6. Symposium fur Experimentelle Urologie, April 15-17, 1982, Bonn, W. Germany. German Association for Urology 155 pp., 1982.

Interferons (IFN) have the ability to stimulate the cytotoxic activity of natural killer (NK) cells. Since NK cells may play a role in the body's defense against tumors, the mechanism of this activation is of interest chiefly in view of the therapeutic applications of IFN. The following investigations analyze the ways in which interferon-ss activates NK cells. Peripheral mononuclear cells (PMC) were isolated from heparinized venous blood of healthy donors by FICOLL-hypaque density gradient centrifugation and incubated on a monolayer of prostatic carcinoma cell line DU 145. The non-adherent PMC were subsequently incubated for 12 h with 1000 IU of IFN-ss/ml medium, and their cytotoxicity against DU 145 determined in a 4 hr 51Cr liberation test. In further experiments a second absorption onto DU 145 monolayers occurred after stimulation with IFN-ss. The cytotoxicity of PMC was completely absorbed during incubation of the PMC on tumor cell layers. A subsequent incubation of the non-adherent PMC with IFN produced a rise in NK cell activity to the pre-absorption level. The IFN-generated cytotoxicity is again absorbed by repeated incubation on a DU 145 tumor cell monolayer. Thus it was possible to show that the transformation of immature NK precursor cells into mature NK cells is induced by stimulation of natural cytotoxicity with IFN-ss. Through this transformation structures are formed on the membrane of NK precursor cells which enable the recognition and binding of target cells. (no Refs) (In GER)

44. SEQUENTIAL ADMINISTRATIONS OF POLYRIBOINOSINIC ACID AND POLYCYTIDYLIC ACID INDUCE INTERFERON AND DEPRESS THE HEPATIC CYTOCHROME P-450-DEPENDENT MONOOXYGENASE SYSTEM.

Deloria LB, Mannering GJ
Dept. Pharmacology, Univ. Minnesota Sch. Medicine, Minneapolis, MN, 55455
Biochem Biophys Res Commun; 106(3):947-952 1982

Injection of 5 mg of single stranded polyriboinosinic acid/kg body wt into male Swiss Random mice followed 1 hr later by injection of 5 mg of single stranded polyribocytidylic acid/kg resulted in losses of ethylmorphine N-demethylase activity and cytochrome P-450 similar to those elicited by 10 mg/kg of double stranded polyriboinosinic.polyribocytidylic acid. Large serum interferon levels were observed after administration of the single-stranded compounds in the same order. When the order was reversed, neither of these effects were observed. (19 Refs)

45. HOMOGENEOUS INTERFERON FROM E. COLI DEPRESSES HEPATIC CYTOCHROME P-450 AND DRUG BIOTRANSFORMATION.

Singh G, Renton KW, Stebbing N
Dept. Pharmacology, Dalhousie Univ., Sir Charles Tupper Medical Building, Halifax, Nova Scotia, B3H 4H7, Canada
Biochem Biophys Res Commun; 106(4):1256-1261 1982

Two highly purified human interferons (IF; LeIF-AD and LeIF-A) and several impure preparations of both mouse and human IF were tested for their ability to depress cytochrome P-450 and dependent drug biotransformation in the liver. The administration of 40,000 units of LeIF-AD resulted in a 47% loss of cytochrome P-450 and 41% loss of cytochrome b5 in microsomes prepared from the livers of BALB c/J mice. Similar losses in cytochrome P-450 and drug biotransformation were also observed in C57BL/6J strain mice treated with LeIF-AD. Changes in the enzyme system were of similar magnitude to those produced by IF inducer poly rI.rC and are equal to the max depression which can be caused by this agent. Similar losses in cytochrome P-450 and related drug metabolism were also observed in mice treated with 50,000 units of impure mouse alpha interferon and beta interferon. The results were in contrast with the highly purified LeIf-A or a crude preparation of human alpha type IF which had no effect on cytochrome P-450 or drug biotransformation. The depression of cytochrome P-450 caused by homogeneous hybrid IF (LeIF-AD) of very high purity provided the first direct evidence that IF can depress the steady state levels of cytochrome P-450 in the liver and result in a loss in the capacity of the liver to metabolize drugs, chemicals, and carcinogens. (20 Refs)

46. MICROINJECTION OF INTERFERON AND 2',5'-OLIGOADENYLATE INTO MOUSE L CELLS AND THEIR EFFECTS ON VIRUS GROWTH.

Higashi Y, Sokawa Y
Dept. Cellular and Molecular Virology, Inst. for Virus Res., Kyoto Univ., Sakyo-ku, Kyoto,, Kyoto 606, Japan
J Biochem (Tokyo); 91(6):2021-2028 1982

By means of a new type of microinjection apparatus, which has a micropipette located in a hole through the optical axis of the condenser lens, we injected interferon (IFN) or 2',5'-oligoadenylate (2-5A) into mouse L cells, and observed their antiviral effects on the multiplication of vesicular stomatitis virus (VSV). After injection, cells were infected with VSV, and labeled with [3H]uridine in the presence of actinomycin D. The proportion of cells infected with VSV which carried radioactive virus-RNA was determined by autoradiography. IFN introduced directly into L cells had no effect on the virus growth. This result supports the idea the IFN molecules exert their effect from outside the cell membrane without penetrating into the cytoplasm. 2-5A, on the other hand, was able to inhibit the growth of VSV effectively when injected into L cells. The antiviral effect was dependent on the dose of 2-5A injected, and moreover the effect was transient, since it disappeared completely after 24-h incubation. (Author abstract) (28 Refs)

47. INTERFERON ENHANCEMENT OF THE INVASIVE CAPACITY OF EWING SARCOMA CELLS IN VITRO.

Siegal GP, Thorgeirsson UP, Russo RG, Wallace DM, Liotta LA, Berger SL

(c/o Berger) Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20205

Proc Natl Acad Sci USA; 79(13):4064-4068 1982

The ability of interferons to reduce cell proliferation in vitro and in vivo is a well-studied phenomenon. To extend such observations, the effect of interferons on the invasiveness in vitro of human malignant cells derived from a Ewing sarcoma was evaluated. Two related parameters were examined: (i) production of Type IV (basement membrane) collagenase and (ii) penetration of human amnion basement membrane and collagenous stroma. After 6 days of treatment with crude fibroblast interferon, leukocyte interferon, or lymphoblastoid interferon at 100 units/ml in serum-free medium, Type IV collagenase levels increased two- to four-fold per cell relative to those of untreated controls. With homogeneous fibroblast and lymphoblastoid interferons, a two-fold elevation in Type IV collagenase was detected after 2 days, with further increases, occasionally dramatic, occurring on the 4th and 6th day of treatment. The ability of Ewing sarcoma cells to invade human amnion connective tissue was measured after 6 days of treatment with various interferons. Relative to the behavior of untreated controls, crude leukocyte interferon, homogeneous lymphoblastoid interferon, and homogeneous fibroblast interferon at 100 units/ml augmented invasiveness 3-, 17-and 22-fold, respectively, when cells were allowed 4 days in which to traverse the amnion. When untreated cells were exposed simultaneously to the amnion and to homogeneous lymphoblastoid or fibroblast interferon, a four- to five-fold increase in invasiveness above control levels was observed in 2 days. These data emphasize the complexity of interferon-induced phenomena. In any overview, the effects of interferon on both the tumor cell and the host must be considered. (Author abstract) (27 Refs)

OTHER RELATED STUDIES

48. THE BIOLOGICAL EFFECTS OF NONIONIZING RADIATION.

Bateman JB

Office Naval Res., London, England

Proceedings of the 10th L.H. Grey Memorial Conference, Held in London, England, July 13-16, 1981. Available from National Technical Information Service, Springfield, VA, as AD-A111 898/3:, 23 pp., 1981.

This is a critical report on the LH Grey Memorial Conference held in Oxford, 13-16 July 1981. The Conference was entitled 'Biological Action of Radiofrequency, Microwave and Ultrasonic Radiations.' The report provides a background identifying the field of interest in broader terms, intended for the general reader. It is then pointed out that the conference was mainly directed toward research and practice related to the possible value of nonionizing radiations in cancer therapy. There were, however, tutorial lectures of a fairly general character and some discussion of biological effects not necessarily arising from production of heat in irradiated tissues. (Author abstract)

49. MOLECULAR ACTIONS AND TARGETS FOR CANCER CHEMOTHERAPEUTIC AGENTS.

Sartorelli AC, Lazo JS, Bertino JR

Dept. Pharmacology, Comprehensive Cancer Center, Yale Univ. Sch. Medicine, New Haven, CT, 06510

Bristol-Myers Cancer Symp Ser 2: 598 pp., 1981.

New approaches to anticancer treatment, important aspects of the molecular actions of anticancer drugs, and possible new biochemical targets for therapeutic agents are discussed. Topics discussed include alkylating agents (molecular mechanisms of cross-linking by alkylating agents and Pt complexes, mechanism of action of antitumor Pt coordination compounds, macromolecular targets and metabolic properties of alkylating drugs, chemotherapeutic approaches to cell populations of tumors, suicide tumor inactivators); antibiotics (DNA dynamics and drug intercalation, molecular pharmacology of anthracyclines, protein antibiotics as DNA-damaging agents, action of bleomycin on DNA); nucleoside analog antimetabolites (transport by animal cells, purine nucleoside phosphorylase and 5'-methylthioadenosine phosphorylase in chemotherapy, effects of 5'thioadenosine nucleosides, locus of action of fluorouracil, inhibition of thymidylate synthetase); folate analog antimetabolites (binding of ligands to dihydrofolate reductase, transport of folate compounds in L1210 cells, membrane transport and molecular basis for antitumor action of folate analogs, cellular mechanisms of resistance to methotrexate); radiation sensitizers (hypoxia-dependent radiation sensitizers and chemotherapeutic agents, mechanistic and pharmacologic considerations); membrane targets (plasma membranes; altered plasma membrane glycoconjugates of Chinese hamster cells with acquired resistance to actinomycin D, daunorubicin, and vincristine; tubulin); and angiogenesis, metastasis, and anticarcinogenesis differentiation (angiogenesis inhibitors, effects of beta-all-trans-retinoic acid on growth and implantation properties of metastatic B16 melanoma cell lines, retinoids and suppression of polypeptide transforming factors, new hematopoietic cell systems, induction of normal differentiation in malignant cells as an approach to cancer therapy). (1112 Refs)

50. GENE AMPLIFICATION.

Schimke RT

Dept. Biological Sciences, Stanford Univ., Stanford, CA

Gene Amplification. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, 339 pp., 1982.

Gene duplication and amplification studies are reviewed and extended abstracts of a conference on gene amplification are presented. Examples of gene amplification include dihydrofolate reductase gene amplification in murine and Chinese hamster ovary cell lines; in a methotrexate-resistant human leukemia cell line (K562); in rat hepatoma cells; in antifolate-sensitive and -resistant Chinese hamster lung cells; in antifolate-resistant, vincristine-resistant, and human neuroblastoma cells; in reciprocally cross-resistant uptake mutants of neuroblastoma; and in vincristine-resistant Chinese hamster ovary cells. Phenotypic reversion as a consequence of gene amplification, altered regulation of the mouse metallothionein-I gene, amplification of the gene for asparagine synthetase, and control of DHFR DNA replication and messenger RNA production. Other aspects of gene amplification are discussed, including studies involving the SEWA mouse tumor, clonogenic human tumor cells, human small cell lung cancer, Drosophila, and chicken actin genes during myogenesis. Molecular structures of amplified DNA structures in mouse cell lines and Chinese hamster ovary cells are described and methods for cloning amplified DNA, analysis of CAD gene amplification, and cloning and analysis of double minute DNA are reviewed. Mechanisms of gene amplification are proposed. Chromosomal alterations are discussed with respect to nonrandom gain of chromosomes in human malignant hematologic diseases, a chromosome defect in most cancers, the biologic role for chromatid exchange in mammalian somatic cells, and a common denominator in the tumorigenic action of viral oncogenes and nonrandom chromosomal changes. (295 Refs)

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EFFECTS OF ANTITUMOR AGENTS ON CELL CYCLE, NUCLEIC ACIDS AND CHROMOSOMES

1. ACTIONS OF CIS-DIAMMINEDICHLOROPLATINUM ON CELL SURFACE NUCLEIC ACIDS IN CANCER CELLS AS DETERMINED BY CELL ELECTROPHORESIS TECHNIQUES.

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Cancer Res; 42(9):3565-3573 1982

Whole-cell electrophoresis determinations were made on a variety of tumor cell suspensions in order to examine the charged groups on the cell surfaces. We report here evidence which indicates the presence of nucleic acids on the surfaces of the tumor cells. Cells of the ascitic and solid forms of the Sarcoma 180 mouse tumor, grown in ICR mice, showed a decrease of 10 to 20% in electrophoretic mobility when incubated with nucleases. One variant, S-180, exhibited sensitivity to RNase only; another variant was sensitive to both RNase and DNase, while different tumor lines were shown to be sensitive

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to DNase only. Treatment of tumor-bearing animals with a therapeutic dose of cisplatin resulted in a loss of tumor cell mobility identical to that produced by the nuclease incubations of the control cells. Incubation of the cisplatin-treated tumor cells with nucleases produced no change in mobility. The isoelectric points of these cells are consistent with the loss of a group with a low pK value in both cisplatin-treated cells and nuclease-incubated cells. Using the S-180 tumor sensitive to both RNase and DNase, the rates of the two enzymes were additive, but the mobility decreased to the same level regardless of whether the enzymes were used alone or together. This suggests that both enzymes act on the same site. RNase and DNase immobilized on agarose beads were capable of lowering the mobility of the cells upon incubation, confirming the surface location of these nucleic acid residues. S-180 tumor cells were also placed in a tissue culture medium at 37 C for up to 22 hr and were treated in vitro with cisplatin and other metabolic inhibitors. Nucleic acid or protein synthesis inhibitors produced a loss of the cell surface nucleic acids. In another in vitro experiment, the nucleic acids were first removed by nucleases, and, when the cells were incubated at 37 C, the nucleic acids reappeared. Disappearance with the inhibitors or reappearance after digestion exhibited a half-time of about 2 hr. Surface nucleic acids were detected by this electrophoresis technique on all of several types of tumor cells but not on any normal cells examined. (18 Refs)

2. HSRS AND DMS IN CELLS WITH ACQUIRED RESISTANCE TO VINCRISTINE (MEETING ABSTRACT).

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Sloan-Kettering Institute for Cancer Research, Rye, NY
Am J Hum Gen; 33(6):5A 1982

It is now well established that the HSRs (homogeneously staining regions) of metaphase chromosomes and DMs (double minutes) can be the sites of amplified DNA sequences encoding dihydrofolate reductase. Most human neuroblastoma cells in culture, although under no obvious selection pressure, such as drug exposure, also exhibit either HSRs or DMs. This observation and additional lines of evidence suggest that the chromosomal anomalies are alternative cytological manifestations of the same phenomenon. Vincristine-resistant cells constitute a newly developed system with similar cytological attributes. Chinese hamster lung cells, DC-3F/VCRd-5, selected by stepwise increase in concentration of vincristine are characterized by an HSR on an abnormal, marker chromosome (9+HSR+Xq). Revertant VCRd-5-U cells maintained in vincristine-free medium showed a decline in resistance and HSR length. Two-dimension (D) gel electrophoresis demonstrated increased synthesis of a 19 KD acidic (pI equals 5.7) protein, designated V19, in the resistant cells. Further, in vitro translation of poly(A) RNA from sensitive, resistant, and revertant cells and 2D gel analysis of the translation products showed a markedly increased synthesis of V19 in DC-3F/VCRd-5 cells, suggesting an increased amount of V19-specific mRNA. Vincristine-resistant human neuroblastoma cells likewise display chromosomal abnormalities as compared to controls. SH-SY5Y/VCR cells are characterized by the presence of 10-100 DMs. The MC-IXC/VCR neurblastoma clone was selected from the parental SK-N-MC line which had a short HSR on a 22q in about 20% of the cells. The vincristine-resistant cells typically contain a new HSR on a 19p. Both drug-resistant human neuroblastoma lines oversynthesize a 26 KD protein, pI 5.7. The HSRs and DMs of the various vincristine-resistant cells appear to represent another example of DNA sequence amplification in response to drug challenge. (no Refs)

3. CYCLIC CHANGE OF DNA FLUORESCENCE INTENSITY OF ADRIAMYCIN-TREATED LEUKAEMIA CELLS IN VITRO (MEETING ABSTRACT).

Takahashi M, Isiglio K
Department of Pathology, Yamaguchi University School of Medicine, Ube, 755, Japan
Cell Tissue Kinet; 15(1):115 1982

L5178Y cells in exponential phase of growth are exposed continuously to 0.5 ug/ml of adriamycin (ADM) and DNA fluorescence distribution was measured at interval by flow cytometric technique combined with a new staining method which utilizes dilute propidium iodide solution (2.5 ug/ml) and which enables differentiation of cells with condensed and decondensed chromatin. From soon after addition of ADM, the cell number ceased increasing due to progressive accumulation of the cells in S and G2 DNA regions lasting for 9 hr. Afterward, the fluorescence distribution became monophasic and the peak channel was subject to a marked cyclic change with a period nearly equal to the cell-cycle time, increasing and decreasing by a factor of two. Scatter volume of the cells also changed periodically in parallel with the fluorescence intensity. Microscopic observation disclosed that these changes can be correlated well with morphologic characteristics of chromatin condensation. (no Refs)

4. COMPARATIVE KINETICS OF POLY(6-THIOINOSINIC ACID) AND 6-MERCAPTOPURINE TREATED L1210 CELLS.

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Cytometry; 3(1):48-54 1982

The synthetic polynucleotide poly(6-thioinosinic acid) (PTA), which has been shown to inhibit L1210 ascites growth in vivo, was compared with 6-mercaptopurine (6MP) for their effects on cellular kinetics of L1210 cells in vitro. These effects were monitored by changes in growth rates, cell volumes and cell-cycle distributions (determined by flow cytometry). Doses are expressed in terms of the purine bases. At the equimolar dose of 0.1 milliM (mM), PTA was more effective than 6MP in reduction of growth rate and total cell number. Reduction of total cell number to the same extent as produced by 0.1 mM PTA, required a concentration of 2.0 mM of 6MP. Concomitant determinations of Coulter volume distributions of cells after exposures of 24 hr or more indicated that 0.1 mM PTA increased av population volumes more than either 0.1 or 2.0 mM 6MP. Neither 6MP nor PTA had much effect on cell-cycle distribution until between 54 and 74 hr of treatment, when both agents produced qualitatively similar changes. Flow sorting of the redistributed populations indicated the increase in vol due to 0.1 mM PTA was almost equally due to an increased percentage of G2 cells and to an increased vol of cells with the G2 DNA content. With 0.1 mM 6MP, increased vol of G2 cells was predominant. Despite its close structural similarities to 6MP, the mechanism of action of PTA remains unknown. (24 Refs)

5. INITIAL STUDIES ON THE MECHANISM OF ACTION OF A NEW, ONCOLYTIC THIAZOLE NUCLEOSIDE, 2-BETA-D-RIBOFURANOSYLTHIAZOLE-4-CARBOXAMIDE (NSC 286193).

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Biochem Pharmacol; 31(14):2371-2380 1982

Studies on the mechanism of action of a new oncolytic nucleoside, 2-beta-D-ribofuranosylthiazole-4-carboxamide, have been undertaken using P388 murine leukemia cells growing in culture. The compound was cytotoxic at micromolar levels, but a number of simple substitutions of both the ring and sugar moieties nullified cytotoxicity. Cytofluorimetric analysis revealed that the drug arrests cells in the 'S phase' of the cell cycle. At antiproliferative concentrations, the agent inhibited the synthesis of both RNA and DNA. When an examination was made of the ability of a comprehensive series of preformed purines and pyrimidines to overcome the inhibition of thymidine incorporation provoked by exposure to the thiazole nucleoside, the guanines were notably effective, but xanthosine also was shown to be an active antidote. Confirmation that the drug was producing a state of guanine deprivation was provided by high performance liquid chromatography (HPLC) analysis of acid-soluble extracts: a time-dependent fall in the concentrations of GMP and GTP ensued upon exposure to the drug; on the other hand, IMP concentrations increased by approx 15-fold. Pursuant to these findings, an examination was made of the enzymologic steps unique to the biosynthesis of guanine nucleotides in cells exposed to cytotoxic concentrations of the drug. No prominent inhibition of GMP synthetase could be demonstrated in vitro or in culture, but the specific activity of IMP dehydrogenase underwent substantial reductions in both of these cases. HPLC analyses of extracts of cultures exposed to supralethal concentrations of the title compound provided evidence of modest anabolism to the 5'-monophosphate among other products; in vitro a chemically synthesized sample of 2-beta-D-ribofuranosylthiazole-4-carboxamide-5' monophosphate was 20x more potent than the parent nucleoside in inhibiting IMP dehydrogenase. On kinetic analysis, this inhibition was non-competitive with IMP as the variable substrate. (15 Refs)

6. TOXICITY OF CISPLATIN AND HYDROXYMALONATODIAMMINE PLATINUM (II) TOWARDS MOUSE BONE MARROW AND B16 MELANOMA IN RELATION TO DNA BINDING IN VIVO.

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Biochem Pharmacol; 31(13):2273-2278 1982

The antitumor selectivity of cisplatin and hydroxymalonatodiammine platinum II (Pt[OHmal(NH3)2]), a second generation platinum drug, was evaluated in C57Bl/Cbi mice bearing advanced intramuscular B16 melanoma. At maximally tolerated doses, Pt[OHmal(NH3)2] produced greater inhibition of growth of the advanced B16 melanoma than did cisplatin. Comparison of dose-response curves for survival of B16 lung colony-forming cells and bone marrow stem cells treated in vivo indicated that selective killing of B16 cells was achieved with Pt[OHmal(NH3)2], whereas cisplatin was relatively nonselective The extent of reaction of platinum with DNA at doses producing measurable levels of survival in tumor and marrow in vivo was similar to values previously observed in cultured cells treated with cisplatin in vitro. Studies of the amount of platinum bound to DNA in tumor and marrow following administration of the two drugs revealed that the improved selectivity of Pt[OHmal(NH3)2] was associated with a selective increase in the amount of platinum bound to tumor DNA, relative to cisplatin. In addition, platinum lesions produced in DNA by Pt[OHmal(NH3)2] appeared to be more effective in producing tumor cell killing than those produced by cisplatin. No significant excision of total DNA-bound platinum from tumor was observed up to 48 hr after administration of either drug. (Author abstract) (16 Refs)

7. ASSOCIATION OF CELL LETHALITY WITH INCORPORATION OF 5-FLUOROURACIL AND 5-FLUOROURIDINE INTO NUCLEAR RNA IN HUMAN COLON CARCINOMA CELLS IN CULTURE.

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Mol Pharmacol; 21(2):468-473 1982

Cytocidal activity of 5-fluorouracil (5-FU) and 5-fluorouridine (5-FUR) was examined by soft agar cloning and the relation of the effects to nucleic acid synthesis and drug incorporation into nuclear RNA was investigated in a human colon carcinoma cell line (HT-29). After 2 hr of drug exposure, 5-FU was toxic only at 10(-3) M whereas almost a 2-log reduction in colony formation was achieved by 10(-5) M 5-FUR. Following a 2-hr or 24-hr exposure to 5-FU and 5-FUR, RNA and DNA syntheses were inhibited in a concentration-dependent manner. The synthesis of low mol wt (4 S) nuclear RNA was not significantly affected by treatment with either drug. No significant difference with the processing of ribosomal RNA (rRNA) was found by long- and short-term exposure to 5-FU and 5-FUR as assessed by lack of accumulation of rRNA greater than 28 S and by inhibition of formation of 28 S and 18 S rRNA. Measurements of the incorporation of [3H]5-FU and [3H]5-FUR into nuclear RNA by agarose gel electrophoresis indicated that 28 S and 18 S rRNA, as well as 4 S RNA, were the main RNA species labeled at noncytotoxic concentrations of drug. At cytocidal drug concentrations, 5-to 10-fold more [3H]5-FU or [3H]5-FUR was incorporated into nuclear 4 S RNA than rRNA. Results indicated that the primary determinant of cell lethality in HT-29 cells is the degree of fluoropyrimidine substitution in nuclear RNA and not inhibition of either DNA or RNA synthesis. (31 Refs)

8. BINDING OF THE ANTICANCER DRUG CIS-DICHLORODIAMMINEPLATINUM TO 3'(2')-GUANOSINE MONOPHOSPHATE AND NUCLEIC ACIDS.

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Anticancer Res; 1(6):383-388 1981

Reaction of 3'(2')-guanosine monophosphate (GMP) with cis-dichlorodiammineplatinum was studied at acidic, neutral, and alkaline pH values. The reaction of GMP with cis-platinum to form Pt(GMP)2 followed by hydrolysis with HClO4 to yield Pt-bis(guanine) [Pt(Gua)2] is presented. Spectral results were expressed in terms of molar absorbances of the monomer (GMP and Gua). Spectra at pH 13 and pH 1 were reversible not only for the control GMP but also for Pt(GMP)2. Thus, exposure to alkali did not cause any irreversible change in the Pt(GMP)2 complex. Platination of the N7 site of GMP did not cause fission of the imidazole ring at alkaline pH. Changes in the spectra of the base Gua on platination at the N7 position observed at acidic, neutral, and alkaline pH values showed many characteristics that were qualitatively similar to those for the N7 alkylation of Gua. Superposed spectra under acidic, neutral, and alkaline conditions are shown for both Pt(Gua)2 and Pt(GMP)2. Except for the degree of separation between the spectra for different pH values, the changes observed for Pt(Gua)2 were similar to those reported for 7-methylguanine obtained by hydrolysis of 7-methyldeoxyguanylic acid. The superposed spectra of Pt(GMP)2 were also similar to those of 7-methylguanine. The results confirmed that the N7 site of the base guanine was blocked by the metal in the reaction of GMP with cis-platinum. (42 Refs)

9. ACTION OF NEOCARZINOSTATIN ON CELL NUCLEI: RELEASE OF SPECIFIC CHROMATIN.

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Biochem Biophys Res Commun; 104(3):889-896 1982

To elucidate the action of neocarzinostatin (NCS) in intact cells, the chromatin structure in which DNA is organized must be considered. A study is presented which shows that NCS produced high double-strand breaks of the DNA and solubilized specific chromatin fragments from nuclei of rat liver. When rat liver nuclei were incubated at 30 C with or without NCS, and the nuclear digest was fractionated in supernatant (S) and pellet fractions, the soluble chromatin increased rapidly during the first 15 min and gradually up to 60 min in the presence of NCS and 2-mercaptoethanol (MP), with little release of acid soluble materials (6% after 60 min). In control samples without NCS or/and MP, much smaller amounts of soluble chromatin were obtained during 60 min of incubation, in which acid-soluble materials increased to 4.5%, which was ascribed to endogenous nuclease. When DNA fragments from NCS-treated nuclei were analyzed by agarose gel electrophoresis, a series of bands with a multiple of monomeric nucleosomal unit was observed, and the ratio of double strand to single strand breaks of DNA in chromatin was high (1:7) as compared with purified DNA (1:30). Hybridization analysis of the DNAs with complementary DNA of liver polysomal polyadenylated messenger RNA showed that NCS solubilized a specific chromatin which differeed from active chromatin which was preferentially excised by micrococcal nuclease. This in vitro action of NCS on chromatin appears to be closely related to its action detected in vivo. (26 Refs)

10. DNA DAMAGE AND SELECTIVE TOXICITY OF DOPA AND ASCORBATE: COPPER IN HUMAN MELANOMA CELLS.

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Cancer Res; 42(9):3783-3788 1982

Six of eight human melanoma lines showed increased sensitivity to killing by dopa and by ascorbate:copper compared with two fibroblast strains and four other human cell lines of nonmelanoma origin. Catechol, epinephrine, and alpha-methyldopa, but not 5,6-dihydroxyindole, exhibited a similar degree of selectivity. Toxicity was greatly reduced when brief exposure times or high cell densities were used. Depending upon culture conditions, melanoma cells accumulated more [3H]dopa- and [14C]ascorbate-derived isotopic label within the first 5 min than fibroblasts, but after 1 hr this difference was less marked. The catalase activity in melanoma cells was not less than that in fibroblasts. Using two independent methods to determine each type of damage, dopa and ascorbate:copper were found to induce DNA breaks in both cell types but not DNA repair synthesis or DNA interstrand cross-links. More DNA breaks were found in melanoma cells (two lines) than in fibroblasts. Semiconservative DNA synthesis was inhibited immediately, recovered within 6 hr, and in melanoma cells was again inhibited after 24 hr. RNA synthesis was inhibited less than DNA synthesis. Human cell lines with differential sensitivity to alpha-radiation, ultraviolet light, cross-linking agents, or monofunctional alkylating agents exhibited normal survival levels when treated with dopa or ascorbate:copper. (Author abstract) (36 Refs)

11. COMPARISON OF THE EFFECTS OF DIHYDROXYANTHRAQUINONE AND ADRIAMYCIN ON THE SURVIVAL OF CULTURED CHINESE HAMSTER CELLS.

Kimler BF, Cheng CC
Radiation Biology Lab., Dept. Radiation Therapy, Univ. Kansas Medical Center, Kansas City, KS, 66103
Cancer Res; 42(9):3631-3636 1982

Dihydroxyanthraquinone [1,4-dihydroxy-5, 8-bis *2-* [*(2-hydroxyethyl)amino*]*ethyl* amino -9,10 anthracenedione (DHAQ) (NSC 279836)] is currently being tested as a cancer chemotherapeutic agent because of its structural similarity to Adriamycin (ADR) and other DNA-intercalating antibiotics. We have therefore studied the effect of DHAQ on the survival of cultured Chinese hamster cells in direct comparison to ADR. Both DHAQ and ADR produced cytotoxicity that was dependent upon the concentration and duration of drug exposure. For 1-hr pulse exposures of asynchronous populations of exponentially growing cells, a 5-to 10-fold greater concentration of ADR than of DHAQ was required to produce the same level of cell killing. There were also differences in the cell cycle age specificity demonstrated by treating at various times before or after selection of cells in mitosis. DHAQ produced the greatest cytotoxicity in cells treated while in G1 or G2; ADR was more effective on cells located in S phase or mitosis. Overall, DHAQ was found to be similar to ADR and other DNA-intercalating antibiotics with regard to the induction of cell lethality. The only differences were those of the concentration required to produce a certain level of effect and of the cell cycle phase specificities for maximum effect. (Author abstract) (34 Refs)

12. INHIBITION OF DNA SYNTHESIS IN MURINE TUMOR CELLS BY GELDANAMYCIN, AN ANTIBIOTIC OF THE BENZOQUINOID ANSAMYCIN GROUP.

Yamaki H, Suzuki H, Choi EC, Tanaka N
Inst. Applied Microbiology, Univ. Tokyo, Tokyo 113, Japan
J Antibiot (Tokyo); 35(7):886-892 1982

The mechanisms of action of geldanamycin, a benzoquinoid ansamycin, was investigated with murine lymphoblastoma L5178Y cells. The agent inhibited the cell growth at concentrations over 0.01 ug/ml. The antibiotic blocked DNA synthesis more markedly than RNA and protein syntheses. Mitosis was not significantly affected by the drug in the cells synchronized with demecolcine (Colcemid). The antibiotic did not interfere with in vitro assembly of tubulin. In the synchronized cells, strong inhibition of DNA synthesis was observed when geldanamycin was introduced into the culture prior to S phase of the cell cycle. The degree of inhibition was stronger with prolongation of incubation period and with increase of DNA synthesis rate. The results suggested that initiation of DNA synthesis or S phase is affected by the drug. DNA degradation was not significantly induced in vivo by the antibiotic. Geldanamycin blocked DNA polymerase alpha more markedly than beta and gamma. The degree of inhibition depended upon concentrations of enzyme but not upon those of template, suggesting a drug-enzyme interaction IC50 for DNA polymerase alpha was 10 ug/ml and for DNA polymerase beta 100 ug/ml at low concentrations of enzyme. The inhibition of DNA polymerase alpha by the antibiotic was non-competitive and Ki was 20 uM. (Author abstract) (16 Refs)

13. THE FORMATION AND RESEALING OF INTERCALATOR-INDUCED DNA STRAND BREAKS IN ISOLATED L1210 CELL NUCLEI.

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Biochem Biophys Res Commun; 107(2):576-583 1982

DNA effects are described of three chemically different intercalating drugs in isolated L1210 cell nuclei: 4'-(9-acridinylamino)-methanesulfon-m-anisidide (m-AMSA), 5-iminodaunorubicin (5-ID), and 2-methyl-9-hydroxyellipticinium (MHE). DNA single-strand breaks (SSB) and DNA-protein crosslinks (DPC) were measured by the alkaline elution technique. m-AMSA and 5-ID produced protein-associated DNA breaks in nuclei but at a lower frequency than in whole cells. The frequency of SSB and DPC induced by the drugs were about equal. While MHE produced SSB in whole cells, no breaks were produced in isolated nuclei. A study of the kinetics of the DNA effects produced by m-AMSA in isolated nuclei indicated that the rapid formation and resealing of DNA breaks were similar to that seen in whole cells. The DNA-protein crosslinks were reversible after removal of m-AMSA. The process by which the reversible, protein-associated DNA strand breaks are produced by intercalating agents may now be studied in an isolated chemical system possessing the breaking-rejoining capacity of whole cells. (12 Refs)

14. MOLECULAR ASSOCIATION BETWEEN DOXORUBICIN (ADRIAMYCIN) AND DNA-DERIVED BASES, NUCLEOSIDES, NUCLEOTIDES, OTHER AROMATIC COMPOUNDS, AND PROTEINS IN AQUEOUS SOLUTION.

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Mol Pharmacol; 22(1):158-165 1982

The ability of doxorubicin (DRN) to form complexes was demonstrated in a nonbiological system by measuring the partition coefficient in a medium of 1-octanol and 0.05 M Tris-distilled water soln and in a biological system by measuring the transmembranous DNR transport and distribution at equilibrium in a medium of human red blood cells and their suspending fluid. Addition of various DNA-derived bases, nucleosides, and nucleotides decreased the partition coefficient of DRN in the nonbiological system, indicating increased hydrophilicity, or decrease of activity in the aqueous phase. Purine derivatives had greater influence than pyrimidine derivatives. The partition coefficient was not affected by temperature (21-60 C) at low DRN concentration in the absence of added compounds; ATP increased the effect of temperature in a concentration-dependent way. The various compounds affected the initial cellular DRN net uptake and equilibrium distribution in red blood cells. ATP decreased both values, and had a more pronounced effect when salt soln was the suspending medium than when cells were in autologous plasma. The activity coefficient of DRN in plasma was 0.15 relative to that in salt soln when activity coefficient was calculated from the apparent permeability coefficient. (30 Refs)

15. EFFECT OF ANTHRACYCLINE ANALOGUES ON THE APPEARANCE OF NEWLY SYNTHESIZED TOTAL RNA AND MESSENGER RNA IN THE CYTOPLASM OF ERYTHROLEUKEMIA CELLS.

Long BH, Willis CE, Prestayko AW, Crooke ST
Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
Mol Pharmacol; 22(1):152-157 1982

Effects of the structural analogs adriamycin (ADM), daunomycin (DNM), carminomycin (CMM), 4-demethoxydaunomycin (4D-DNM), pyrromycin (PYM), marcellomycin (MCM), and aclacinomycin (ACM) upon total RNA synthesis and appearance of total RNA and polyadenylated (poly(A)+)-RNA in the cytoplasm of uninduced Friend erythroleukemia cells were studied. Each drug was tested at six different concentrations and compared with the av of two controls in three separate experiments. Generally, there were greater differences between the effects of different drugs than were exhibited by the same drug upon the different RNA populations. The differences were clearer when expressed as median dose (IC50) values. The Class II anthracyclines, MCM and ACM, inhibited RNA synthesis by 50% at 60 nanoM, which is 20-50 fold lower than the IC50 value for class I anthracyclines, DNM and ADM. Inhibition of the appearance of poly(A)+-RNA in the cytoplasm closely paralleled inhibition of total RNA synthesis for ADM, DNM, and CMM, whereas the appearance of poly(A)+-RNA was less sensitive to inhibition by the Class II drugs. IC50 values for inhibition of the appearance of total RNA into the cytoplasm were consistently 1/2 to 1/3 the respective IC50 values for total cellular RNA synthesis inhibition, suggesting that one possible factor in the effects of these anthracyclines is alteration of post-transcriptional events. Pre-messenger RNA and pre-ribosomal RNA effects probably play a minor role in inhibiting the appearance of RNA in the cytoplasm compared to the activity at the transcriptional level. (30 Refs)

16. A REASSESSMENT OF THE MECHANISM OF ACTION OF 4'-[(9-ACRIDINYL)-AMINO]METHANESULFON-M-ANISIDIDE.

Marshall B, Ralph RK
Dept. Cell Biology, Univ. Auckland, Auckland, New Zealand
Eur J Cancer Clin Oncol; 18(6):553-557 1982

The conclusion that treating cells with 4'-[(9-acridinyl)-amino]methanesulfon-m-anisidide (mAMSA) causes an alkali-dependent decrease in the size of their DNA was reinvestigated. Evidence is presented that alkali is not needed to detect an effect of mAMSA on the sedimentation rate of DNA released from mAMSA-treated PY815 cells and that mAMSA causes double-strand breaks in cellular DNA. (Author abstract) (17 Refs)

17. SENSITIVITY TO 1-(4-AMINO-2-METHYL-5-PYRIMIDINYL)METHYL-3-(2 CHLOROETHYL)-3-NITROSOUREA HYDROCHLORIDE (ACNU) OF GLIOMA CELLS IN VIVO AND IN VITRO.

Yoshida J, Shibuya N, Kobayashi T, Kageyama N
Dept. Neurosurgery, Nagoya Univ. Sch. Medicine, 65, Tsuruma-cho, Show-Ku, Nagoya, Japan
Cancer; 50(3):410-418 1982

A new water-soluble nitrosourea (1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2 chloroethyl)-3-nitrosourea hydrochloride, ACNU) was tested for its antitumor activity against four glioma cell lines. Four factors were studied to determine its antitumor activity: inhibition of cell growth, morphologic observation, analysis of DNA histogram with flow microfluorometry, and sensitivity testing with microtest plate. Growth inhibition in response to ACNU was seen in two cell lines (EA-285, U251-MG), whereas two cell lines (YE2-2, T98) were resistant to ACNU. The results of the present sensitivity test concur with those of other examinations that this test is useful in selecting a drug and determining the effective dose. (Author abstract) (21 Refs)

OTHER CELLULAR AND SUBCELLULAR EFFECTS OF ANTITUMOR AGENTS

18. MONITORING THE EFFECT OF ANTI-CANCER DRUGS ON L1210 CELLS BY A MITOCHONDRIAL PROBE, RHODAMINE-123.

Bernal SD, Shapiro HM, Chen LB
Sidney Farber Cancer Inst., Harvard Medical Sch., 44 Binney St., Boston, MA, 02115
Int J Cancer; 30(2):219-224 1982

The cancer chemotherapeutic agents 1-beta-D-arabinofuranosylcytosine (Ara-C), methotrexate, and 5-fluorouracil cause a rapid loss of mitochondrial Rh-123 uptake in L1210 cells, which correlates with the loss of clonogenic ability. The loss of Rh-123 uptake is irreversible and occurs prior to Trypan Blue staining. Thus, the antimetabolites, unlike freeze-thawing and detergent treatments, generally cause mitochondrial damage prior to changes in plasma membrane permeability. Since the effect of antimetabolites on Rh-123 uptake is maximal at 24 hr, the Rh-123 assay may provide a rapid alternative to the clonogenic assay for monitoring the cytotoxic effects of these drugs. Our results also suggest that the inhibition or impairment of mitochondrial function may be an important step in the cytocidal and/or cytostatic action of anti-cancer drugs. (Author abstract) (25 Refs)

19. ENHANCEMENT OF HUMAN CHORIONIC GONADOTROPHIN PRODUCTION BY ANTIMETABOLITES.

Browne P, Bagshawe KD
Dept. Medical Oncology, Charing Cross Hosp., Fulham Palace Road, London W6 8RF, England
Br J Cancer; 46(1):22-29 1982

The action of methotrexate, actinomycin D, bleomycin, vincristine and hydroxyurea on the production of human chorionic gonadotrophin (hCG) by a choriocarcinoma cell line (BeWo) has been studied. hCG production per unit of cell protein was increased, and this was a continuing process only halted by cell death. The proportion of hCG-producing cells in the population increased from approx 5% to a max of approx 40% during incubation with vincristine. A possible explanation for these and related observations is that cytotoxic agents promote the differentiation of cytotrophoblast to syncytium. A similar mechanism could contribute to the unusual sensitivity of choriocarcinoma to cytotoxic agents. (Author abstract) (23 Refs)

20. INTERACTION OF VINBLASTINE WITH STEADY-STATE MICROTUBULES IN VITRO.

Wilson L, Jordan MA, Morse A, Margolis RL
Dept. Biological Sciences, Univ. California, Santa Barbara, CA, 93106
J Mol Biol; 159(1):125-149 1982

At low concentrations, vinblastine binds rapidly and reversibly to a very limited number of high affinity sites on steady-state bovine brain microtubules (mean Kd, 1.9 x 10(-6) M; 16.8 +-4.3 vinblastine binding sites per microtubule) which appear to be located at one or both ends of the microtubules. At high concentrations, vinblastine binds to a high binding capacity class of sites of undetermined affinity, located on helical strands of protofilaments which form at the ends of depolymerizing microtubules, and/or along the surface of the microtubules. Substoichiometric inhibition of microtubule assembly, which occurs at low vinblastine concentrations, appears to be due to the binding of vinblastine to the high affinity class of sites. Fifty percent inhibition of tubulin addition to the net assembly ends of steady-state microtubules occurred at 1.38 x 10(-7) M-drug, and at this concentration, 1.16 +-0.27 molecules of vinblastine were bound to the high affinity class of sites. Vinblastine appeared to bind directly to the microtubule ends, and our results indicate that vinblastine inhibits the assembly of steady-state bovine brain microtubules by binding rapidly and with high affinity to one or two molecules of tubulin at the net assembly ends. Splaying and peeling of protofilaments at microtubule ends and the active depolymerization of microtubules occurred only at vinblastine concentrations greater than 1 x 10(-6) to 2 x 10(-6) M. This action of vinblastine is associated with, and may be due to, the binding of vinblastine to the high capacity class of sites. Both actions of vinblastine may be due to the binding of vinblastine to the same binding sites on the tubulin molecule, with the sites exhibiting either a high or low affinity depending upon the location in the microtubule. (Author abstract) (43 Refs)

21. EFFECT OF METHOTREXATE ON DIHYDROFOLATE REDUCTASE ACTIVITY IN METHOTREXATE-RESISTANT HUMAN KB CELLS.

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Mol Pharmacol; 21(2):478-482 1982

A cloned human cell variant derived from KB cells which exhibits unique behavior since its resistant phenotype has both stable and an unstable component, the former being independent of exogenous methotrexate (MTX), was studied. A comparative analysis of the properties of both parental KB cells, the MTX-resistant subline 6b, and the purified dihydrofolate reductase (DHFR) isolated from these two lines was performed. The KB/6b subline had a 40-fold elevation of DHFR (in the absence of MTX), and this increase was accompanied by a 6,500-fold resistance to MTX. Following the removal of MTX from KB/6b cells, the actual DHFR specific activity decreased. The apparent half-life of DHFR was 11.5 hr for cells in the presence or absence of MTX. Cells depleted of MTX were re-exposed to MTX concentrations ranging from 0.25 uM to 75 uM for 48 hr. DHFR specific activity increased with increasing MTX concentration up to 2.5 uM. The results further supported the conclusion that induction of enzyme in the cells is probably due to enzyme stabilization by MTX. When cycloheximide was added simultaneously with MTX, the MTX induction of DHFR activity was prevented. In contrast, actinomycin D added simultaneously with MTX had no effect on the MTX induction of DHFR activity. Results suggested that modulation of DHFR specific activity by MTX occurs at either the translational level or by unidentified post-transcriptional mechanism(s). (19 Refs)

22. IN VITRO BIOLOGICAL ACTIVITY OF 9-BETA-D-ARABINOFURANOSYL-2-FLUOROADENINE AND THE BIOCHEMICAL ACTIONS OF ITS TRIPHOSPHATE ON DNA POLYMERASES AND RIBONUCLEOTIDE REDUCTASE FROM HELA CELLS.

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Mol Pharmacol; 21(2):474-477 1982

Suitability of 9-beta-D-arabinofuranosyl-2-fluoroadenine (2-F-araA) as a substrate for cytoplasmic deoxycytidine (dCyd) kinase and for mitochondrial pyrimidine deoxynucleoside (dPyd) kinase was examined utilizing highly purified enzymes from human leukemic blast (HeLa) cells. 2-F-araA was inhibitory to the growth of HeLa cells in culture and the concentration for a 50% inhibition (I50) was 0.25 uM. The drug was less effective against the replication of herpes simplex virus Type 1 and 2 and was inhibitory only at concentrations that were toxic to host cells (5 uM). As compared with dCyd at a concentration of 0.4 milliM (mM), 2-F-araA (0.4 mM) was a good substrate for the cytoplasmic dCyd kinase but was a poor substrate for the mitochondrial dPyd kinase. At identical deoxynucleoside triphosphate concentrations, the 5'-triphosphate of 2-F-araA (2-F-araATP) was much more inhibitory to DNA alpha-polymerase than to beta-polymerase. 2-F-araATP strongly inhibited ADP reductase and cytidine diphosphate reductase activities with I50 values of 1 uM and 8.5 uM, respectively. The inhibition by 2-F-araATP of DNA alpha-polymerase and ribonucleotide reductase suggested that 2-F-araATP may exert its action through a 'self-potentiation' mechanism by decreasing deoxyATP formation. (16 Refs)

23. INHIBITION OF GLYCOLYSIS OF MAMMALIAN CELLS BY MISONIDAZOLE AND OTHER RADIOSENSITIZING DRUGS. PREVENTION BY THIOLS.

Varnes ME, Biaglow JE
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Biochem Pharmacol; 31(14):2345-2351 1982

Prolonged anaerobic incubation of Ehrlich ascites tumor cells and Chinese hamster V79-379A cells with misonidazole, desmethylmisonidazole, or niridazole led to inhibition of both glucose consumption and lactate formation. This effect was measured in cells washed free of the nitro compounds and resuspended in fresh buffer or medium. The degree of inhibition of glucose utilization was related to drug concentration, and to the rate of metabolic reduction, as measured under aerobic conditions by KCN-insensitive oxygen consumption. Misonidazole-induced inhibition of glycolysis developed concurrently with depletion of intracellular non-protein thiol (NPSH) and was protected against by the presence of cysteamine, cysteine and, to some extent, GSH in the cell incubate. These findings suggest reaction of reduced drug intermediates with thiol-containing enzymes. The glutathione-reactive agent diethyl maleate was used to deplete 90% of the endogenous NPSH, but this depletion did not alter the effects of misonidazole on glycolysis. (Author abstract) (29 Refs)

24. RETINOIC ACID INDUCES EMBRYONAL CARCINOMA CELLS TO DIFFERENTIATE INTO NEURONS AND GLIAL CELLS.

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Dept. Biology, Univ. Ottawa, Ottawa K1N 6N5, Canada
J Cell Biol; 94(2):253-262 1982

Murine embryonal carcinoma cells can differentiate into a varied spectrum of cell types. We observed the abundant and precocious development of neuronlike cells when embryonal carcinoma cells of various pluripotent lines were aggregated and cultured in the presence of nontoxic concentrations of retinoic acid. Neuronlike cells were also formed in retinoic acid-treated cultures of the embryonal carcinoma line, P19, which does not differentiate into neurons in the absence of the drug. The neuronal nature of these cells was confirmed by their staining with antiserum directed against neurofilament protein in indirect immunofluorescence experiments. Retinoic acid-treated cultures also contained elevated acetylcholinesterase activity. Glial cells, identified by immunofluorescence analysis of their intermediate filaments, and a population of fibroblastlike cells were also present in retinoic acid-treated cultures of P19 cells. We did not observe embryonal carcinoma, muscle, or epithelial cells in these cultures. Neurons and glial cells appeared in cultures exposed to retinoic acid for as little as 48 hr. We found no evidence for retinoic acid toxicity, suggesting that the effect of the drug was to induce the development of neurons and glia rather than to select against cells differentiating along other developmental pathways. (Author abstract) (49 Refs)

25. STUDIES ON VARIOUS PARAMETERS INFLUENCING LEUKEMIC CELLS DESTRUCTION BY ALKYL-LYSOPHOSPHOLIPIDS.

Andreesen R, Modolell M, Oepke GH, Common H, Lohr GW, Munder PG
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Anticancer Res; 2(1/2):95-100 1982

Direct cytotoxicity of alkyl-lysophospholipids (ALP) was studied and parameters necessary for the induction of leukemic cell destruction were evaluated. The effect of different serum concentrations on the cytotoxicity of 1-octadecyl-2-methyl-glycero-3-phosphocholine (ET-18-OCH3) on human leukemic cells was studied. Variations in the serum concentration influenced the effect of a constant amount of ET-18OCH3 on the proliferation of tumor cells. In the presence of 40% fetal calf serum, human leukemic cells were only slightly affected. When natural 2-lysophosphatidylcholine was added in increasing amounts to cultures at a constant serum concentration of 10%, the addition resulted in a similar decrease and retardation of ET-18-OCH3 induced cell destruction as was observed with the increasing serum concentration. The addition of 1-octadecyl-glycero-3-phosphocholine (ET-18-OH) also antagonized the destructive effect of ET-18-OCH3. Temperature and pH of the culture medium had a strong influence on leukemic cell destruction. A strong decrease in cell destruction was observed after a temperature decrease of 2 C (37-35 C), while a 2 C increase (37-39 C) resulted in a marked potentiation of cell destruction. When vincristine and ALP, in concentrations which have no toxic effect, were added simultaneously to the cultures, a complete leukemic cell destruction was observed. Inhibition of ALP cytotoxicity was observed when cells were precultured with sterols for 24 hr or when sterols and ALP were added simultaneously to the cultures. Addition of sterols after ALP induced cell destruction exhibited no effect. (30 Refs)

26. CYTOSTATIC ACTIVITY AND METABOLIC EFFECT OF N-TRICHLOROMETHYLTHIO-4-CYCLOHEXANE-1,2-DICARBOXIMIDE ON EHRLICH ASCITES CARCINOMA CELLS.

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Neoplasma; 29(2):205-214 1982

Effect of N-trichloromethylthio-4-cyclohexane-1,2-dicarboximide (NTCD) on energy-yielding and energy-requiring processes in Ehrlich ascites carcinoma (EAC) cells has been investigated. At concentrations higher than 10 ug/ml NTCD causes a rapid and practically full inhibition of both aerobic glucose uptake and lactate formation. On the other hand, at concentrations lower than 10 ug/ml, these metabolic parameters are stimulated. The stimulation of glycolysis, according to our previous results, suggests the interference of NTCD with mitochondrial functions. This image is supported by the marked inhibitory effect of NTCD on respiration of isolated mitochondria. The inhibition of glycolysis with higher concentrations of NTCD is the consequence of inactivation of hexokinase (EC 2.7.1.1), eventually of 6-phosphofructokinase (FC 2.7.1.11). The described effects of NTCD are given into coherence with chemical modification of appropriate functional SH groups of EAC cells by the compound studied. Proportionally to the dose and time NTCD inhibits the synthesis of macromolecules in whole EAC cells as measured by the incorporation of labeled adenine and valine into the TCA-insoluble fractions. The inhibition of biosynthetic processes followed is the consequence of exclusion of key processes in the energy metabolism and leads to the loss of EAC cells transplantability. (Author abstract) (28 Refs)

27. ANTITUMOR AGENTS LIV: THE EFFECTS OF DAPHNORETIN ON IN VITRO PROTEIN SYNTHESIS OF EHRLICH ASCITES CARCINOMA CELLS AND OTHER TISSUES.

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J Pharm Sci; 71(7):745-749 1982

Daphnoretin has been shown to suppress Ehrlich ascites carcinoma growth in mice. One of the modes of action of the drug is to block protein synthesis; however, the inhibition of protein synthesis requires a higher concentration of drug than the inhibition of DNA synthesis. The inhibition of protein synthesis appears to occur during the elongation step with the drug preferentially binding to free ribosomes not engaged in active protein synthesis. (Author abstract) (23 Refs)

28. DIFFERENTIAL EFFECTS OF ANTHRACYCLINE DRUGS ON RAT HEART AND LIVER MICROSOMAL REDUCED NICOTINAMIDE ADENINE DINUCLEOTIDE PHOSPHATE-DEPENDENT LIPID PEROXIDATION.

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Cancer Res; 42(9):3574-3582 1982

Rat liver microsomes have previously been utilized as a model biological system to study the activation of Adriamycin to the semiquinone free radical intermediate and the enhancement by Adriamycin of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidation and oxygen consumption. Incubating rat liver microsomes with Adriamycin or other structurally similar benzanthraquinone anticancer drugs resulted in marked stimulation of NADPH-dependent lipid peroxidation. Carminomycin and 4-demethoxydaunorubicin were considerably more potent than Adriamycin, while daunorubicin, deacetyladriamycin, N-dimethyl-adriamycin, aclacinomycin A, adriamycin 14-nicotinate, and steffimycin were approx equipotent to Adriamycin in this test system. In contrast, lapachol, anthragallol, aklylaminoanthracenedione, mitomycin C, streptonigrin, 5-iminodaunorubicin, and the Adriamycin:DNA complex potently inhibited microsomal lipid peroxidation. Methotrexate, cyclophosphamide, 5-fluorouracil, nogalamycin or rubidazone had little or no effect. alpha-Tocopherol-deficient rat heart microsomes but not control microsomes were susceptible to increased NADPH-dependent lipid peroxidation when incubated with Adriamycin or other anthracycline analogs which stimulated peroxidation in liver microsomes. The rate of NADPH oxidation in the presence of microsomes was was enhanced four-fold by either Adriamycin or daunorubicin; lapachol, anthragallol, aminoanthracenedione, and 5-iminodaunorubicin at concentrations which inhibited lipid peroxidation had no effect on NADPH oxidation. NADPH:cytochrome P-450 reductase activity was unaltered by those drugs which either stimulated or inhibited peroxidation. These results suggest that although several Adriamycin-like anthracycline drugs dramatically stimulated NADPH-dependent, reactive oxygen-mediated lipid peroxidation in rat liver and heart microsomes, other quinone-containing anticancer drugs do not enhance lipid peroxidation. There appears to be a direct correlation between the ability of certain anthracyclines to stimulate heart or liver microsomal lipid peroxidation and the effects of these drugs in other cardiotoxicity model systems. (Author abstract) (48 Refs)

29. DEMONSTRATION THAT THE TEMPORARY SEQUESTERING OF ADVENTITIOUS IRON ACCOUNTS FOR THE INHIBITION OF MICROSOMAL LIPID PEROXIDATION BY BLEOMYCIN A2.

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Res Commun Chem Pathol Pharmacol; 37(1):21-31 1982

One of the manifestations of the interaction of bleomycin with the microsomal mixed-function oxidase system is an inhibition of NADPH- dependent, reactive oxygen-mediated lipid peroxidation. The results of this investigation demonstrate that this effect by bleomycin can be attributed to the sequestering of adventitious iron. However, as a result of the microsome-catalyzed, iron-facilitated activation of bleomycin and the concomitant spontaneous decay of the activated bleomycin intermediate, iron can apparently no longer be bound by the bleomycin molecule; consequently, the inhibition of microsomal lipid peroxidation by bleomycin is only temporary. (Author abstract) (16 Refs)

30. ANTITUMOR ACTIVITY AND HYDROGEN PEROXIDE RELEASE BY MACROPHAGES ELICITED BY TREHALOSE DIESTERS.

Lepoivre M, Tenu JP, Lemaire G, Petit JF
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J Immunol; 129(2):860-866 1982

Trehalose diesters (natural 6,6'-trehalose dimycolate from Mycobacterium tuberculosis) or synthetic (a 76 carbon atom analogue), when suspended in water, gives stable and well-defined emulsions. These emulsions, injected ip in mice significantly limit the growth of P815 syngeneic mastocytoma cells. They elicit macrophages with a cytostatic activity against P815 cells in vitro, strong enough to be expressed at low effector to target ratios (E/T = 1.4) or after a short coincubation period (2 hr). The antitumor potential of these macrophages seems to coincide with their ability to release H_2O_2 upon pharmacologic triggering. Depressed levels of alkaline phosphodiesterase and beta-galactosidase are proposed as other biochemical markers of cytostatic macrophages. (Author abstract) (44 Refs)

31. EFFECTS OF CYCLOPHOSPHAMIDE ON MURINE BONE MARROW AND SPLENIC MEGAKARYOCYTE-CFC, GRANULOCYTE-MACROPHAGE-CFC, AND PERIPHERAL BLOOD CELL LEVELS.

Yeager AM, Levin FC, Levin J
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J Cell Physiol; 112(2):222-228 1982

The effect of cyclophosphamide (CY) on megakaryocytopoiesis in C57BL/6J mice was investigated by serially determining alterations of megakaryocyte colony-forming cells (CFC) derived from the marrow and spleen following ip administration of 200 mg/kg CY. Platelet count showed rebound thrombocytosis after 11 days, while neither hematocrit values nor the total WBC counts exhibited rebound increments during recovery from CY. A decrease in the number of megakaryocyte-CFC (MEG-CFC) was observed in the bone marrow at 24-48 hr after CY, and a rebound increase occurred thereafter and was maximal at 5 days; at 7 days, splenic MEG-CFC were strikingly increased following an initial 5-day period of suppression. Both time and magnitude of the responses to CY of both MEG-CFC and granulocyte-macrophage CFC (GM-CFC) in the mouse marrow were similar. MEG-CFC and GM-CFC of bone marrow and splenic origin differed significantly in their response to CY; in the spleen, both showed similar patterns of recovery after exposure to CY (substantially decreased through day 5) while both had shown maximal rebound increases in the marrow by day 5. The maximal rebound increase in splenic MEG-CFC and GM-CFC occurred by day 7, when marrow-derived precursors had already returned to the normal range. Thus, MEG-CFC and GM-CFC in mouse bone marrow and spleen demonstrated significant differences in time, magnitude, and duration of response to CY, while the responses of these CFC were similar within specific organs. It is suggested that increased platelet counts in CY-treated mice may be attributable, at least in part, to alterations in feedback mechanisms which control megakaryocytopoiesis, thereby stimulating the megakaryocyte progenitor compartment. (35 Refs)

FACTORS INFLUENCING SENSITIVITY TO ANTITUMOR AGENTS

32. DIFFERENTIAL PROTECTION AGAINST ALKYLATING AGENT INJURY IN TUMOR AND NORMAL TISSUES (MEETING ABSTRACT).

Phillips TL, Yuhas JM
No affiliation given
First Conference on Radioprotectors and Anticarcinogens, June 21-24, 1982, Washington, DC. National Bureau of Standards 41 pp., 1982.

In our laboratory we have carried out a series of experiments investigating the effect of WR-2721 on the response of intestinal crypt cells, bone marrow CFUs cells, and the EMT6 mouse mammary carcinoma. Using the maximally tolerated dose of adriamycin, bleomycin, BCNU (carmustine), cis-platinum, cyclophosphamide, 5-fluorouracil, L-phenylalanine mustard, methotrexate and nitrogen mustard, the response of CFUs (colony-forming units) crypt cells and tumor were evaluated. Not all drugs were used in each tissue because in some cases no response to particular agents were observed in one of the three tissues. Chemoprotection of the bone marrow CFUs at 50% survival level ranged from a high of a DMF of 10 for cyclophosphamide to a low of 1.0 for 5-fluorouracil. All of the alkylating agents were protected against, as was adriamycin, to a certain extent in the CFU assay. Using the intestinal crypt cell assay, dose modifying factors (DMF) of 1.3 were seen for adriamycin and BCNU at a survival of 10 crypts, whereas the DMF was 1.8 for cis-platinum and 2.0 for melphalan and nitrogen mustard. No protection was seen against 5-fluorouracil and methotrexate damage. Protection against the effect of cytotoxic agents on the regrowth of the EMT6 tumor was absent for all of the alkylating agents tested, including nitrogen mustard, BCNU, cyclophosphamide, and cis-platinum. There was also no protection against the cell kill induced in the tumor by 5-fluorouracil. (no Refs)

33. RADIOPROTECTION OF NORMAL TISSUES AND TUMORS (MEETING ABSTRACT).

Denekamp J, Michael BD, Rojas A, Stewart FA
Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, England
First Conference on Radioprotectors and Anticarcinogens, June 21-24, 1982, Washington, DC. National Bureau of Standards 191 pp., 1982.

The amino-thiol WR-2721 has been studied as a radioprotective compound in seven different normal tissue systems and in three transplantable tumor lines at Gray Laboratory. Dose response curves have been constructed for animals treated in the presence or absence of 400 mg/kg WR-2721 and protection factors have been derived from the iso effective x-ray doses. In normal tissues a wide range of protection factors has been obtained, ranging from 1.3 in lung and kidney to 2.2 for skin clones. The protection factors are generally independent of the size of the x-ray dose or are reduced at the low x-ray doses. The protection factors in the three tumors ranged from 1.0 to 2.8, with a marked dependence on the size of the x-ray dose, particularly when single doses and fractionated treatments are compared. The tumor protection is most noticeable at low x-ray doses. These results indicate that WR-2721 is not selective in its radioprotective action on normal tissues. We suggest that the results can be explained in terms of the cellular oxygen concentration in the target cells. A diminution of the radioprotective action of WR-2721 has also been seen in both skin and tumors if misonidazole is added instead of excess oxygen or if high LET (linear energy transfer) radiation is used. These results are explicable in terms of competition for fixation and restitution of the initial radiation damage. (no Refs)

34. THE DIFFERENTIAL PROTECTION BY WR-2721 OF HAIR AND SKIN VERSUS GROWING CARTILAGE AND BONE FOLLOWING IRRADIATION IN WEANLING RATS (MEETING ABSTRACT).

Constine LS, Rubin P, Poulter CA
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Twenty-fourth Annual Meeting of the American Society of Therapeutic Radiologists, October 25-29, 1982, Orlando, Florida American Society of Therapeutic Radiologists; 1982

WR-2721 was given intraperitoneally to CrL:CD(SD)BR female rats establishing an LD50/30 of 466 mg/kg body weight. The left tibiae of four 12 animal groups were treated with single doses of 600, 1200, 1800 and 2400 rad respectively. Identically treated groups were administered 310 mg/kg WR-2721 (2/3 the LD50/30) in a concentration 26 mg/ml intraperitoneally 15 minutes prior to irradiation. Rats untreated or given WR-2721 without radiation served as control groups. Radiographs of the irradiated and unirradiated tibiae for each animal were obtained weekly to the date of sacrifice at 80 days following the initial treatment. Skin toxicity was assessed weekly using Moulder's scale starting on the second week. No significant difference in bone growth as measured by tibiae lengths for the protected and unprotected animals was observed. Skin toxicity including moist desquamation occurred in irradiated limbs. Protected rats exhibited substantially less skin toxicity and epilation than unprotected rats. We conclude that WR-2721 as administered has no significant radioprotective effect on tibial growth in weanling rats, but substantially reduces the accompanying skin toxicity and hair loss. (no Refs)

35. THE RADIOPROTECTION OF PARENCHYMAL HEPATOCYTES WITH WR-2721 (MEETING ABSTRACT).

Jirtle RL, Noell KT
Duke University Medical Center, Durham, NC
Twenty-fourth Annual Meeting of the American Society of Therapeutic Radiologists, October 25-29, 1982, Orlando, Florida American Society of Therapeutic Radiologists; 1982

The successful treatment of metastatic and primary tumors of the liver with ionizing radiation is limited by the radiosensitivity of the surrounding normal parenchymal tissue. To investigate the radiation survival characteristics of liver we developed an in vivo clonal assay system for parenchymal hepatocytes. The survival curve for noncycling hepatocytes irradiated with low LET (linear energy transfer) radiation has been shown to possess a relatively small shoulder even after potentially lethal damage is repaired. This indicates that parenchymal hepatocytes may be relatively more sensitive than malignant cells to conventional fractionated radiotherapy treatment. The radioprotective agent WR-2721 has been reputed to selectively protect normal tissues and to concentrate in the liver. Based upon this information we initiated studies to determine to what extent WR-2721 protects parenchymal hepatocytes from radiation damage. Female Fischer 344 syngeneic rats were given an IP injection of WR-2721 (400 mg/kg) 30 min prior to 60Co irradiation. In order to allow for potentially lethal damage repair the hepatocytes were assayed for cell survival 24 hrs after irradiation. The results of this study demonstrate that in the liver WR-2721 acts as a dose modifying agent with a DMF of approximately 2.1. Thus, the Dq and D0 values for hepatocytes irradiated in the presence of WR-2721 were increased from 220 to 470 cGy and 270 to 570 cGy, respectively. If malignant cells are not protected to the same extent, WR-2721 could provide a significant selective radioprotection of the liver during fractionated treatment of primary and metastatic lesions. (no Refs)

36. RADIOSENSITIZATION OF HYPOXIC TUMOR CELLS BY DEPLETION OF INTRACELLULAR GLUTATHIONE.

Bump EA, Yu NY, Brown JM
Div. Radiobiology Res., Dept. Radiology, Stanford Univ. Medical Center, Stanford, CA, 94305
Science; 217(4559):544-545 1982

Depletion of glutathione in Chinese hamster ovary cells in vitro by diethylmaleate resulted in enhancement of the effect of x-rays on cell survival under hypoxic conditions but not under oxygenated conditions. Hypoxic EMT6 tumor cells were similarly sensitized in vivo. The action of diethyl maleate is synergistic with the effect of the electron-affinic radiosensitizer misonidazole, suggesting that the effectiveness of misonidazole in cancer radiotherapy may be improved by combining it with drugs that deplete intracellular glutathione. (Author abstract) (9 Refs)

37. PHOTOSENSITIZED DEGRADATION OF DNA BY DAUNOMYCIN.

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Photochem Photobiol; 36(1):49-57 1982

Visible irradiation of DNA-daunomycin solutions resulted in a decrease of viscosity of the DNA and an increase of the rate of denaturation of DNA in formaldehyde. These changes are consistent with the induction of single-strand breaks in the DNA, some of which pair to cause fragmentation of the DNA. The DNA damage increases with drug:nucleotide ratio up to 0.2 and is diminished beyond that range. The damage also increases with ionic strength up to 0.6 M and is diminished above that value. These results suggest that the non-intercalated form of the drug is involved in the photosensitization process. Radicals that are produced accompanying the degradation have been trapped by 5,5-dimethyl-1-pyrroline-1-oxide and identified as hydroxyl radicals from their ESR spectrum. The DNA photosensitized damage is completely inhibited when hydroxyl radicals are removed by the spin-trap, suggesting a direct role for the hydroxyl radicals in the DNA photosensitized degradation process. The implications of the photosensitized DNA damage and the production of hydroxyl radicals in this process are discussed with respect to the medical uses and chemotherapeutic role of daunomycin. (Author abstract) (47 Refs)

38. TOXICITY OF POLYALKYLCYANOACRYLATE NANOPARTICLES II: DOXORUBICIN-LOADED NANOPARTICLES.

Couvreur P, Kante B, Grislain L, Roland M, Speiser P
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J Pharm Sci; 71(7):790-792 1982

The possibility of significantly reducing toxicity of an anticancer drug such as doxorubicin by fixing it on polyisobutylcyanoacrylate nanoparticles was studied. It was shown that, when the drug was adsorbed on nanoparticles, significant reduction of both mortality and wt loss of mice were recorded under various administration schedules. Furthermore, cardiotoxicity was decreased due to the poor uptake by the myocardium. (Author abstract) (7 Refs)

39. CHANGES IN THE PHARMACOKINETICS OF METHOTREXATE BY ENCAPSULATION IN LIPOSOMES AND THE VARYING EFFECT ON EXPERIMENTAL TUMORS.

Freise J, Diehl V
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Onkologie; 4(1):4-5 1981

The effects of encapsulation of methotrexate in liposomes on the pharmacokinetics and therapeutic effect of the drug were studied in mice bearing experimental Ehrlich ascites tumors. In comparison with free methotrexate or NaCl control injections, methotrexate in liposomes significantly reduced the number of ascites cells by a factor of 3-4. A review of literature indicates that encapsulation slows excretion of methotrexate and increases the amount of the drug that concentrates in tumor tissues. (6 Refs) (In GER)

40. GROWTH STATE-SPECIFIC RESPONSIVENESS OF PRIMARY CULTURES OF A NUDE MOUSE-XENOGRAFTED HUMAN COLON CARCINOMA TO 4'-DEOXYDOXORUBICIN AND A CRUDE HUMAN LEUKOCYTE ALPHA-INTERFERON PREPARATION.

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Cancer Res; 42(9):3789-3792 1982

Improved procedures for the seeding of primary cultures from human colon tumors are described. Responsiveness of primary cultures from human colon carcinoma T348 to a crude preparation of human leukocyte alpha-interferon and a DNA-intercalating experimental anticancer drug, 4'-deoxydoxorubicin, has been investigated. The effect of the interferon preparation on such cultures is shown to be growth state specific; ie, stationary populations are killed, whereas fast-growing cultures are reversibly growth inhibited by the same doses of interferon. In contrast, 4'deoxydoxorubicin kills growing populations, whereas stationary cultures are barely affected by the same concentration of this drug. Interferon antagonizes the cytotoxic effect of 4'deoxydoxorubicin on a growing colon tumor cell population when applied immediately after 4'-deoxydoxorubicin treatment. Implications of this finding for the combined application of several drugs in cancer therapy are discussed. (Author abstract) (11 Refs)

41. TENIPOSIDE (VM-26)- AND ETOPOSIDE (VP-16-213)-INDUCED AUGMENTATION OF METHOTREXATE TRANSPORT AND POLYGLUTAMYLATION IN EHRLICH ASCITES TUMOR CELLS IN VITRO.

Yalowich JC, Fry DW, Goldman ID
(c/o Goldman) Dept. Medicine, Medical Coll. Virginia, Richmond, VA, 23298
Cancer Res; 42(9):3648-3653 1982

Teniposide (VM-26) and etoposide (VP-16-213) were evaluated for their effects on methotrexate transport and metabolism in Ehrlich ascites tumor cells in vitro. VM-26 (10 uM) does not alter influx of methotrexate but slows efflux of the drug which leads to an increase in the steady-state level of exchangeable antifolate. VM-26 stimulation of net methotrexate transport occurs within 5 min of exposure of cells to VM-26 concentrations of from 10 to 50 uM; removal of extracellular VM-26 results in a rapid and complete reversal of this effect. As extracellular VM-26 is raised to 50 uM, the progressive rise is net methotrexate uptake observed is due not only to elevated exchangeable antifolate but to an enlarged nonexchangeable pool of intracellular drug as well, a major portion of which is methotrexate polyglutamyl derivatives. VM-26 does not alter the intracellular water or the chloride distribution ratio. Glucose partially reverses the stimulatory effect of VM-26 but to a lesser extent than glucose reversal of the vincristine-induced stimulation of net methotrexate transport. VP-16-213 also stimulates net methotrexate transport in a manner qualitatively similar to that of VM-26. However, 100 uM VP-16-213 is required to yield the same quantitative stimulation as seen for 10 uM VM-26. VP-16-213-induced augmentation of intracellular methotrexate polyglutamate levels is also demonstrated. These results indicate that VM-26 and VP-16-213 enhance net cell accumulation of methotrexate and methotrexate polyglutamyl derivatives in the Ehrlich ascites tumor in vitro at concentrations of these agents which are achieved in vivo. Potential therapeutic synergism between methotrexate and epipodophyllotoxins on this basis is therefore possible and is currently under evaluation in animal tumor systems. (Author abstract) (36 Refs)

42. POTENTIATION OF THE ANTIMITOCHONDRIAL AND ANTIPROLIFERATIVE EFFECTS OF BIS(GUANYLHYDRAZONES) BY PHENETHYLBIGUANIDE.

Byczkowski JZ, Zychlinski L, Porter CW

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Cancer Res; 42(9):3592-3595 1982

The ability of methylglyoxal-bis(guanylhydrazone) (MGBG) and 4,4'-diacetyldiphenylurea-bis(guanylhydrazone) to interact with the hypoglycemic agent, phenethylbisguanide (DBI), in affecting the bioenergetic functions of isolated rat liver mitochondria was studied. DBI was found to increase markedly the inhibitory effect of either 4,4'-diacetyldiphenylurea-bis(guanylhydrazone) or MGBG on respiration of isolated rat liver mitochondria. Conversely, these bis(guanylhydrazones) enhanced the inhibitory potency of DBI and increased the apparent affinity of mitochondria for the drug. As with MGBG and 4,4'-diacetyldiphenylurea-bis(guanylhydrazone), the potassium cationophore, valinomycin, increased the sensitivity of mitochondrial respiration to DBI. It is suggested that the enhancement of bis(guanylhydrazone) inhibition of mitochondrial respiration by DBI involves inhibition of proton fluxes across the inner mitochondrial membrane and the subsequent alkalinization of the mitochondrial matrix. This drug interaction was extended to the level of antiproliferative activity in which DBI was found to potentiate the growth-inhibitory effect of MGBG on murine L1210 leukemia in vivo. (Author abstract) (37 Refs)

43. INCORPORATION OF THE ANTITUMOR ALKALOID THALIBLASTINE IN LIPOSOMES ENHANCES ITS CYTOTOXIC ACTIVITY IN VITRO.

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Dept. Physiology, Univ. Athens Medical Sch., Athens 609, Greece

Experientia; 38(7):857-859 1982

The incorporation of the antitumor alkaloid thaliblastine in liposomes greatly enhances its cytotoxicity in Walker S and TLX-5 cell cultures. (Author abstract) (24 Refs)

44. THE EFFECT OF MISONIDAZOLE ON THE CYTOTOXICITY AND DNA CROSS-LINKING ACTIVITY OF AN ACTIVATED SULFIDOCYCLOPHOSPHAMIDE IN HYPOXIC MOUSE LEUKEMIA CELLS.

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Mol Pharmacol; 22(1):175-181 1982

Synergistic toxicity of misonidazole (MISO) and 4-S-(propionic acid)-sulfidocyclophosphamide (C-2) was demonstrated by measurements of colony-forming ability of hypoxic mouse L1210 leukemia cells, and the effect of MISO on DNA cross-linking capabilities of C-2 were studied. At various concentrations of C-2, cell kill of hypoxic L1210 cells from 2.5 milli(m)M MISO was enhanced in relation to C-2 concentration. With concentrations of MISO from 2.5 to 20 mM with 10 uM C-2 the toxicity of C-2 was enhanced by increasing MISO levels. Alkaline elution profiles were used to assess the degree of interstrand cross-linking occurring in L1210 DNA following exposure to 300 rads x-rays in the presence of 10 uM C-2, 2.5 mM MISO, or the combined drugs at these concentrations. MISO alone produced few if any DNA single-strand breaks, whereas C-2 and C-2 + MISO caused cross-linking, with a greater frequency for the combination of two agents than for C-2 only. Cross-linking was highest approx 6 hr after exposure, with almost complete removal of cross-links in DNA by 15 hr. The enhancement of C-2 toxicity by MISO yields effects beyond the additive effects alone. The fact that cross-linking effects of C-2 were not immediate in the presence of MISO suggests that enhanced transport of C-2 is not the mechanism of potentiation; rather it seems to be an effect on the action at the DNA target, which may be the mechanism in potentiation of other chemotherapeutic drugs by MISO. (30 Refs)

45. INCREASED ENHANCEMENT OF TUMOUR RESPONSE TO X-RAYS AND HIGH-LET NEON IONS BY DESMETHYLMISONIDAZOLE RELATIVE TO MISONIDAZOLE.

Tenforde TS, Curtis SB, Parr SS, Afzal SM, Howard J, Lyman JT
Biology and Medicine Div., Lawrence Berkeley Lab., Univ. California, Berkeley, CA, 94720
Int J Radiat Biol; 41(6):677-684 1982

Relative effectiveness of misonidazole (MISO) and desmethylmisonidazole (DMMISO) was tested for the enhancement of tumor growth delay when used in combination with high-linear-energy-transfer (-LET) radiation from neon ions in the extended-peak ionization region. DMMISO exerted a significantly greater radiosensitizing effect than MISO when these components were administered at their max tolerated ip dose levels to WAG/Rij rats. The increase in dose enhancement ratios for DMMISO relative to MISO was similar with low-LET and high-LET neon ions in the extended-peak ionization region. (14 Refs)

TRANSPORT, BINDING, CONVERSION AND METABOLISM OF ANTITUMOR AGENTS

46. A KINETIC ANALYSIS OF THE UPTAKE OF 5'-DEOXY-5-FLUOROURIDINE IN EHRLICH ASCITES TUMOR CELLS (MEETING ABSTRACT).

Enigbokan MA, Bowen D
Department of Pharmacology, Howard University, Washington, DC, 20059
Med Pediatr Oncol; 10(1):99 1982

The time course of uptake of a new cytotoxic agent 5'-deoxy-5-fluorouridine (5'dFUr) was determined at 37 degrees in unperturbed Ehrlich tumor cells. Short term uptake studies were determined by a rapid sampling technique which allows sampling of cell suspensions at intervals as short as 0.5 sec. The time course of 5'dFUr uptake is composed of an initial rapid uptake component which appears to represent a surface adsorption of the drug. This is followed by a slower uptake component of 5'dFUr which is constant for 20 sec and represents the unidirectional influx process. Transport across the cell membrane occurs by a carrier mechanism displaying an apparent Km of 38 uM and a Vmax of 1.52 nmoles/g dry wt/sec. Dipyridamole, a nucleoside transport inhibitor, inhibits 5'dFUr influx. Influx of 5'dFUr was inhibited by the homologous nucleosides, fluorouridine (FUr) and fluorodenoxyuridine (FUdR). Transstimulation of 3H-FUr, 3H-FUdR, and 3H-5'dFUr is demonstrated when cells are loaded with 5 mM nonlabeled 5'dFUr. Hence, these data suggest the transport of 5'dFUr utilizes a mobile carrier system similar to fluoropyrimidine nucleosides and, therefore, maybe a model substrate for the study of fluorinated nucleoside transport. (no Refs)

47. THE METABOLISM OF PROCARBAZINE IN ISOLATED RAT HEPATOCYTES.

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Diss Abstr Int [B]; 42(10):3963-B 1982

The effect of animal pretreatment on the appearance of azoprocarbazine and N-isopropylterephthalamic acid in the blood stream following ip injection of procarbazine was measured. Both phenobarbital and 5,6-benzoflavone decreased the blood levels of azoprocarbazine, indicating rapid further metabolism. Phenobarbital pretreatment increased the rate of appearance of N-isopropylterephthalamic acid, but at 30 minutes the level in the blood was the same for all animals. The rate of oxidation to azoprocarbazine by hepatocytes from untreated animals compared favorably with the rate for microsomal incubations. Pretreatment of animals with phenobarbital enhanced this rate 2-fold, but 5,6-benzoflavone had no effect. The rate of N-isopropylterephthalamic acid formation was more sensitive to 5,6-benzoflavone than phenobarbital animal pretreatment. Sonicated hepatocytes oxidized procarbazine to azoprocarbazine in the absence of added NADPH, suggesting a non-cytochrome P-450 activity was contributing to the oxidation. This activity was localized to the mitochondrial fraction, an azoprocarbazine was found by HPLC (high performance liquid chromatography) analysis to be the only organic-soluble product of mitochondrial procarbazine metabolism. Measurements of the rates of formation of methane from procarbazine, azoprocarbazine, the hydrazone and monomethylhydrazine suggested that any methane generated from cellular or microsomal incubations with procarbazine occurred via a pathway which included all the above compounds. The effects of inhibitors and induction on methane formation from azoprocarbazine and monomethylhydrazine, and the failure to demonstrate methane as a product of the metabolism of either azoxyprocarbazine isomer, supported this hypothesis. (no Refs)

48. EFFECTS OF ADRENAL CORTICAL STEROIDS AND OSMOTIC BLOOD-BRAIN BARRIER OPENING ON METHOTREXATE DELIVERY TO GLIOMAS IN THE RODENT: THE FACTOR OF THE BLOOD-BRAIN BARRIER.

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Proc Natl Acad Sci USA; 79(14,part1):4420-4423 1982

The effect of adrenal cortical steroids and osmotic blood-brain barrier modification on methotrexate delivery to normal and glioma-bearing rats was studied. In animals with the avian sarcoma virus-induced glioma, osmotic blood-brain barrier modification resulted in significantly increased delivery of methotrexate to the tumor-bearing hemisphere (including the tumor, the brain around the tumor, and the brain distant to the tumor), compared to the nonmodified hemisphere or to control animals. The administration of adrenal steroids, followed by intracarotid methotrexate, resulted in slightly decreased chemotherapeutic agent (methotrexate) delivery to the tumor, the brain around the tumor, and the brain distant to the tumor. When adrenal steroids were given prior to barrier modification and methotrexate therapy, the level of methotrexate was significantly less in the tumor. These studies provide evidence that the blood-brain barrier exists in tumors and is a factor in drug delivery to tumors. Steroid administration greatly interferes with the enhancement of drug delivery to tumors that can be achieved with osmotic blood-brain barrier modification. (Author abstract) (17 Refs)

49. TUMORICIDAL EFFECT OF MACROPHAGES EXPOSED TO ADRIAMYCIN IN VIVO OR IN VITRO.

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Cancer Res; 42(9):3851-3857 1982

Peritoneal macrophages from BD IX rats collected 24 hr after an ip injection of Adriamycin (10 mg/kg) were cytotoxic to syngeneic cancer cells in culture. In contrast, incubation in vitro in Adriamycin solutions did not evoke tumoricidal activity in peritoneal macrophages, whatever the incubation time (from 1 to 24 hr) and the Adriamycin concentration (from 1 ng to 100 ug/ml). Macrophages incubated with Adriamycin in vitro accumulated the drug in their nuclei, whereas macrophages from animals receiving Adriamycin in vivo accumulated it in cytoplasmic vacuoles. Early observation of peritoneal cells after in vivo exposure to Adriamycin shows that Adriamycin is concentrated in mast cell granules which are released and then phagocytosed by peritoneal macrophages. Mast cells exposed to Adriamycin in vitro can induced macrophages to become cytotoxic. These facts explain the difference between macrophages exposed to Adriamycin in vivo and in vitro. Adriamycin fluorescence appears in nuclei of cancer cells incubated with in vivo-labeled macrophages, suggesting that macrophages can directly transfer the drug into cancer cells and therefore play a role in the Adriamycin antitumor effect. (Author abstract) (22 Refs)

50. METABOLISM AND MECHANISMS OF ACTION OF 9-(TETRAHYDRO-2-FURYL)-6-MERCAPTOPURINE IN CHINESE HAMSTER OVARY CELLS.

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Chem Biol Interact; 41(1):105-115 1982

The mechanisms of action of 9-(tetrahydro-2-furyl)-6-mercaptopurine (THFMP) have been studied in Chinese hamster ovary (CHO) cells in tissue culture. THFMP is relatively unstable in physiological buffers, being facilely converted to 6-mercaptopurine (6-MP) even in the absence of cells. Consequently, THFMP undergoes metabolic conversions characteristic of 6-MP, namely formation of 6-thioIMP and incorporation into DNA as 6-thioguanine (6-TG) nucleotide. A number of purines are capable of preventing the toxicity of THFMP in wild-type cells in a manner similar to that of 6-MP. However, exogenous purines and pyrimidines did not prevent the toxicity of THFMP to cells deficient in the enzyme, hypoxanthine-guanine phosphoribosyltransferase (EC 2.4.2.8; HGPRTase). Cells lacking HGPRTase were 20-40-fold resistant to 6-TG and 6-MP but were only 2-4-fold resistant to THFMP. Furthermore, the time-course for killing CHO cells deficient in HGPRTase was different from that in wild-type cells containing the enzyme. There was no apparent effect of THFMP on the utilization of precursors for DNA, RNA or protein synthesis in the enzyme-deficient mutant cell line. The results suggest that THFMP is converted non-enzymatically to 6-MP and shares its mechanisms of action in wild-type cells containing HGPRTase, ie, inhibition of de novo purine biosynthesis and incorporation into DNA as 6-TG nucleotide. However, the mechanism of action of THFMP in cells lacking HGPRTase is probably unique and is presently unknown. (Author abstract) (22 Refs)

51. THE MECHANISM OF RENAL CLEARANCE OF CISPLATIN (CIS-DICHLORODIAMMINE PLATINUM II) AND ITS MODIFICATION BY FUROSEMIDE AND PROBENECID.

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Biochem Pharmacol; 31(13):2243-2246 1982

When isolated rat kidneys are perfused with 30uM cisplatin there is net tubular transport of platinum, resulting in excretion of platinum at a rate 125% of the rate attributable to glomerular filtration alone. Probenecid and furosemide are drugs which have been reported to protect against cisplatin nephrotoxicity, by unknown mechanisms. When probenecid 0.3 mM is included in the perfusate net transport of platinum is increased to 200% of that accounted for by glomerular filtration alone. Increasing the concentration of probenecid to 3.0 mM does not significantly further increase the rate of excretion of platinum. The inclusion of furosemide 0.3 mM in the perfusate has no effect on the net tubular transport of platinum. However, at 3.0 mM furosemide causes a decrease in the net platinum transport and only 93% of platinum filtered at the glomerulus appears in the urine. Thin-layer chromatography revealed the presence of at least three platinum compounds in the urine in addition to cisplatin. We conclude that the renal excretion of cisplatin and its transformation products, even in this model system, is a complex process involving glomerular filtration, tubular excretion and tubular reabsorption. (Author abstract) (20 Refs)

52. DEGRADATION OF MELPHALAN IN AQUEOUS SOLUTIONS - INFLUENCE OF HUMAN ALBUMIN BINDING.

Ehrsson H, Lonroth U
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J Pharm Sci; 71(7):826-827 1982

The protein binding and degradation rate of melphalan in human albumin solutions and plasma have been investigated. In plasma, melphalan is bound 69.0 +-3.4% (25 C, melphalan concentration 25 ug/ml). The stability of melphalan when bound to albumin is about 3x higher (k = 3.07 x 10(-2) +-0.48 x 10(-2) hr-1) than unbound in solution (k = 1.14 x 10(-1) +-0.01 hr-1). (Author abstract) (5 Refs)

53. CONCENTRATION-DEPENDENT DISAPPEARANCE OF FLUOROURACIL FROM PERITONEAL FLUID IN THE RAT: EXPERIMENTAL OBSERVATIONS AND DISTRIBUTED MODELING.

Collins JM, Dedrick RL, Flessner MF, Guarino AM
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J Pharm Sci; 71(7):735-738 1982

The rate of disappearance of fluorouracil from peritoneal fluid has been experimentally measured and mathematically modeled. The experimental data were obtained following the installation of 50 ml of dialysis fluid which contained an initial fluorouracil concentration ranging from 24 uM to 12 mM. The rate of disappearance was strongly dependent upon concentration. A distributed model has been formulated which incorporates concepts of diffusion with saturable metabolism and nonsaturable capillary uptake in the tissue surrounding the peritoneal fluid. This model successfully describes the experimental observations and also suggests that the effective penetration depth into tissue is highly dependent upon concentration. (Author abstract) (20 Refs)

54. MODULATION OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE METABOLISM AND CYTOTOXICITY IN L1210 CELLS BY FLUOROPYRIMIDINE PRETREATMENT.

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Cancer Res; 42(9):3550-3556 1982

The effect of pretreatment with the fluoropyrimidines 5-fluorouracil (FUra), 5-fluorouridine (FUrd), 5-fluoro-2'-deoxyuridine (FdUrd), and 5'-deoxy-5-fluorouridine (5'dUrd) on the intracellular metabolism and in vitro cytotoxicty of 1-beta-D-arabinofuranosylcytosine (ara-C) was explored in L1210 cells. A 4-hr exposure to 100 uM FUra, FUrd, or FdUrd produced greater than 3-fold increments in the intracellular accumulation of [3H]deoxyctidine, and 2-fold increments in the intracellular accumulation of [3H]ara-C were produced over a 1-hr exposure. Intracellular 1-beta-D-arabinofuranosylcytosine 5'-triphosphate levels in cells exposed to these three agents were also increased over 2-fold. L1210 cells exposed sequentially to 1 uM FUra, FUrd, or FdUrd followed by 5 uM ara-C for 1 hr resulted in synergistic cell killing measured by soft-agar cloning. Although intracellular 2'-deoxycytidine 5'-triphosphate levels were reduced in cells treated for 4 hr with FUra and FUrd, this was not associated directly with the maximum accumulation of ara-C. FdUrd treatment was as effective as FUra and FUrd at enhancing ara-C accumulation and 1-beta-D-arabinofuranosylcytosine 5'-triphosphate formation and producing synergistic cytotoxicity; however, the 2'-deoxycytidine 5'-triphosphate pools were minimally affected. 5'-Deoxy-5-fluorouridine did not increase intracellular ara-C accumulation, reduce-intracellular 2'-deoxycytidine 5'-triphosphate levels, or enhance ara-C cytotoxicity. This sequential drug interaction is similar to that which we have observed when methotrexate precedes ara-C and provides a rational basis from which further in vivo studies can be designed. (Author abstract) (36 Refs)

55. TUMOR AFFINITY AND DNA INTERACTIONS OF 57CO-BLEOMYCIN.

Kakinuma J, Honjo Y, Orii H
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Radioisotopes; 31(4):175-178 1982

Tumor affinity of two isomeric forms of 57Co-bleomycin (BLM) was studied in Rous sarcoma-bearing SR-DDD-Br mice with respect to distribution of the Type I and Type II isomers in the tumor, blood, muscles, liver, and kidneys. DNA binding properties of the isomers were studied with the aid of DNA melting. Accumulation in the tumor tissues and stability of DNA binding of Type I isomer were higher than those of Type II. (5 Refs) (In JPN)

STRUCTURE-ACTIVITY STUDIES OF ANTITUMOR AGENTS

56. CORRELATION OF ANTITUMOR ACTIVITY AND ELECTRON DEFICIENCY OF NITROFURANYLHYDRAZONE COMPOUNDS.

Newman RA, Strauss MJ, Renfrow R
Vermont Regional Cancer Center, Univ. Vermont, Burlington, VT, 05405
J Pharm Sci; 71(7):831-832 1982

Phenylhydrazone derivatives of 5-nitro-2-furaldehyde were tested for antitumor activity against L-1210 murine leukemia in vitro. A substantial increase in antitumor activity was observed in these series of compounds as the electron deficiency of the six-membered aromatic ring was increased. A possible mechanism of action involving drug reduction as well as antibacterial and antitumor efficacy is discussed. (Author abstract) (19 Refs)

57. CONFORMATION OF NUCLEOSIDES AND NUCLEOTIDES, ROLE IN SOME ENZYMATIC REACTIONS, AND RELEVANCE TO DESIGN OF ANTITUMOR AND ANTIVIRAL AGENTS.

Shugar D, Stolarski R, Dudycz L
Inst. Biochemistry and Physics, Acad. Sciences, 02-532 Warszawa, Poland
Excerpta Med Int Congr Ser; 571:74-83 1982

Many proposals relating solid state and soln conformations to biological activity suffer from the assumption that these are the predominant or preferred conformations, overlooking the possible interaction of a given analogue with a target site, eg, that an enzyme or coenzyme, may involve conversion to other allowable conformations, normally present in a small amount in soln, and not at all in the solid state. Practical examples are presented which utilize a promising new approach to drug-receptor interactions which is based on the use of computer-assisted modeling systems. Discussions involving original studies and contributions from the literature are presented on interactions of NAD positive analogues with dehydrogenases, orotidine-5'-phosphate decarboxylase (OMPD), 5'-nucleotidase, nucleoside phosphorylases, and adenosine deaminase. Four schemes are illustrated. One scheme illustrates conformations of adenine and nicotinamide moieties of the glycosidic bonds in NAD+. A second deals with a procedure for evaluation of the syn and anti conformer populations of purine (adenine in the example) nucleosides, based on the relative chemical shift of H(2') with respect to the shifts for model analogues in the fixed syn (1 example) and anti (3 examples) conformations. A third scheme outlines presumed structures and conformations of inhibitors of OMPD prior to and after binding to the enzyme. The fourth scheme deals with nucleoside substrates of uridine phosphorylase. (31 Refs)

EFFECTS OF ANTIMETASTATIC AGENTS

58. IMPROVEMENT OF RADIATION TREATMENT OF ARTIFICIAL AND SPONTANEOUS LUNG METASTASES IN MICE BY COMBINATION OF THE TREATMENT WITH MISONIDAZOLE AND ACTINOMYCIN-D (MEETING ABSTRACT).

Wondergem J, Haveman J

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Int J Radiat Biol; 42(1):73 1982

Artificial lung metastases were obtained by injecting mice intravenously (iv) in the tail with tumor cells derived from a transplantable murine mammary adenocarcinoma (M8013X). Inoculation with 10(4) viable cells led to death of the mice as a result of lung metastases between day 25 and 35. To study the effects of radiation treatments of lung metastases, mice were irradiated on the thorax, at different time intervals after inoculation. Administration of the hypoxic cell sensitizer misonidazole always increased the effects of irradiation with regard to the number of animals cured. However, misonidazole did not lead to a tumor growth delay and thus to a delay in the death of animals which were not cured. Combination of the radiation treatment with the anticancer drug actinomycin-D increased the effects of irradiation with regard to the number of animals cured. However, misonidazole did not lead to a tumor growth delay and thus to a delay in the death of animals which were not cured. Combination of the radiation treatment with the anticancer drug actinomycin-D increased the effect of the treatment both with regard to the number of cures and to tumor growth delay. Tumors of this transplantable adenocarcinoma located in the hind leg of mice metastasized spontaneously to only the lungs at volumes of the primary tumor larger than 200 mm3. When the primary tumor was cured by irradiation and misonidazole 30 per cent of the animals died from metastases, whereas 20 percent of the animals died when the primary tumor was cured by radical surgery. When the lungs were irradiated early after iv injection of tumor cells in the tail or after cure of the primary tumor, the number of metastases found after autopsy was relatively small. These results show that combination of radiation treatment of lung metastases with misonidazole or actinomycin-D may lead to favorable results at doses tolerated by the lungs. (no Refs)

59. TUMOR CELL-PLATELET AGGREGATION: INDUCED BY CATHEPSIN B-LIKE PROTEINASE AND INHIBITED BY PROSTACYCLIN.

Honn KV, Cavanaugh P, Evens C, Taylor JD, Sloane BF

Dept. Radiology, Wayne State Univ., Detroit, MI, 48202

Science; 217(4559):540-542 1982

The ability of tumor cells to metastasize may be related to their ability to promote aggregation of host platelets. The use of inhibitors of cysteine proteinases resulted in parallel inhibition of B16 amelanotic melanoma-induced platelet aggregation and of cathepsin B activity. The antimetastatic agent prostacyclin inhibited platelet aggregation induced by the tumor cells and by papain, a cathepsin B-mimicking agent. (Author abstract) (34 Refs)

SYNTHESIS, ISOLATION, CHARACTERIZATION AND ANALYSIS OF ANTITUMOR AGENTS

60. PARTIAL CIRCUMVENTION OF RESISTANCE TO 6-MERCAPTOPURINE BY ACYLATED P1,P2-BIS(6-MERCAPTOPURINE-9-BETA-D-RIBOFURANOSIDE-5') PYROPHOSPHATE DERIVATIVES.

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Cancer Res; 42(9):3769-3775 1982

P1,P2-Bis(6-mercaptopurine-9-beta-D-ribofuranoside-5') pyrophosphate [trivial name, bis(thioinosinate) (bis(MPRP))] and its butyryl and hexanoyl derivatives [P1-,P2-bis(O2',O3'-diacyl-6-mercaptopurine-9-beta-D ribofuranoside-5') pyrophosphate] were synthesized by established procedures. The inhibitory effects of bis(MPRP) on cell proliferation in cultures of D98, Chinese hamster lung, L1210 cells, and thiopurine-resistant sublines were determined. Bis(MPRP) exhibited greater activity than did 6-mercaptopurine against resistant D98 cells but was approx equivalent to 6-mercaptopurine or 6-mercaptopurine riboside (MPR) with all other lines. Extracellular degradation of bis(MPRP) by L1210 cells was monitored by high-performance liquid chromatography. The compound was cleaved slowly to MPR and MPR diphosphate in contrast to the rapid extracellular dephosphorylation of MPR monophosphate. Acylated bis(MPRP) derivatives were developed on the basis that bis(nucleotide) compounds capable of entering cells and releasing nucleoside diphosphates might conceivably overcome ribosyltransferase and increase in alkaline phosphohydrolase activities. Unlike bis(MPRP), P1,P2,bis(O2', O3'-dibutyryl-6-mercaptopurine-9-beta-D-ribofuranoside 5') pyrophosphate and P1,P2-bis(O2',O3'-dihexanoyl-6-mercaptopurine-9-beta-D ribofuranoside-5') pyrophosphate were less inhibitory than MPR towards parent L1210 cells but were far more active than the riboside against an MPR-resistant subline. The culture growth-inhibitory activity of the acylated derivatives was considerably greater than could possibly be accounted for by the release of the carboxylic acids. Therefore, it is suggested that partial circumvention of thiopurine resistance may have resulted from cellular uptake of intact acylated bis(MPRP) molecules. (Author abstract) (24 Refs)

61. ANTILEUKEMIC AND CYTOTOXIC CONSTITUENTS OF DIRCA OCCIDENTALIS (MEETING ABSTRACT).

Badawi MM, Handa SS, Kinghorn AD, Cordell GA, Farnsworth NR

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Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburg, Pennsylvania American Society of Pharmacognosy; :A76 1982

A chloroform extract of the twigs and flowers of Dirca occidentalis Gray (Thymelaeaceae), collected in California, was found to possess both in vivo and in vitro activity in the P-388 test system. Bioassay-directed fractionation afforded two antileukemic daphnane esters, Pimelea factor P2 and dircin, a new compound. A further four constituents of this species, the three lignans, (-)-medioresionol, (+)-syringaresinol and (-)-lariciresinol, as well as the coumarin, daphnoretin, were found to exhibit cytotoxic activity. (no Refs)

62. ANTITUMOR MACROMOLECULAR SUBSTANCE FROM LITTLENECK CLAM, MERCENARIA MERCENARIA (MEETING ABSTRACT).

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Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburg, Pennsylvania American Society of Pharmacognosy; :A70 1982

We reported that some marine invertebrates contain tumor inhibitory substances in their macromolecular fractions. An extract of littleneck clam, M mercenaria, was one of the four promising samples in the investigation. The water extract was fractionated by ultrafiltration, and the fraction of molecular weight larger than 300,000 daltons, which showed a strong antitumor activity against sarcoma 180, was chromatographed on DEAE (diethylaminoethyl)-Sepharose CL-6B. The partially purified antitumor active fractions from DEAE-chromatography showed an inhibitory effect on complement dependent hemolysis in vitro. The activity was higher than the well-known antitumor polysaccharides, zymosan and lentinan. We will discuss a further purification and partial characterization of this antitumor substance. (no Refs)

63. ADDITIONAL NEW MAYTANSINOIDS FROM TREWIA NUDIFLORA: 10-EPITREWIASINE AND NORTREWIASINE (MEETING ABSTRACT).

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Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburg, Pennsylvania American Society of Pharmacognosy; :A67 1982

Previously we have described the isolation and characterization of six new maytansinoids from Trewia nudiflora L (Euphorbiaceae). These compounds, the most abundant of which is trewiasine, have potent tumor-inhibiting properties in experimental systems as well as a variety of insect-control properties. Further work has revealed two additional members of this series--10-epitrewiasine and nortrewiasine. Isolation of these new maytansinoids was achieved by HPLC (high pressure liquid chromatography), and structures were elucidated by high-field proton NMR (nuclear magnetic resonance) C-13 NMR, EIMS, and negative ion CIMS. (no Refs)

64. NORMAYTANCYPRINE, A NEW MAYTANSINOID FROM PUTTERLICKIA VERRUCOSA (MEETING ABSTRACT).

Sneden AT

Department of Chemistry, Virginia Commonwealth University, Richmond, VA

Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburgh, Pennsylvania American Society of Pharmacognosy; :A37 1982

Normaytancyprine, a new antileukemic maytansinoid, was isolated from Putterlickia verrucosa Szyszyl (Cellstraceae). Elucidation of the structure of normaytancyprine was accomplished by a combination of chemical and spectroscopic methods. The mass spectrum and 1H NMR (nuclear magnetic resonance) spectrum indicated that normaytancyprine was an 18-N-demethylmaytanside ester. Hydrolysis of normaytancyprine followed by preparation of the p-bromobenzyl ester of the side chain acid defined the structure of the side chain as an N-acyl derivative of N-methyl-l-alanine. Finally, comparison of the 13C NMR spectra of normaytancyprine with the spectra of other maytansinoids defined the structure of the N-acyl group. The isolation and structure elucidation of normaytancyprine, its antileukemic activity, and its relationship to other antileukemic ansa macrolides will be discussed. (no Refs)

65. PINOCEMBRIN AND GONIOTHALAMIN, TWO BIOACTIVE COMPONENTS FROM GONIOTHALAMUS GIGANTEUS (ANNONACEAE) (MEETING ABSTRACT).

Ebrahim AA, Ferrigni NR, McCloud TG, Cassady JM, Chang CJ, McLaughlin JL

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Twenty-third Annual Meeting of the American Society of Pharmacognosy, August 1-5, 1982, Pittsburgh, Pennsylvania American Society of Pharmacognosy; :A20 1982

Antitumor fractionation of the title plant produced fractions which were consistently toxic to mice in the 3PS assay. F008 (90% MeOH, toxic at 6.25 mg/kg) showed antitumor activity in the crown gall potato disc assay and was also toxic (LC50 215 ppm) to brine shrimp (less than 1000 ppm is considered 'active'). Column chromatography of F008 on silica gel yielded four zones of brine shrimp activity. From the first zone (LC50 less than 10 ppm), the known compounds, (-)-pinocembrin (5,7-dihydroxyflavanone) and goniothalamin (3-ene-5-styryl-2-pyrone) were isolated and identified; both were toxic to brine shrimp. Additional bioassays and fractionations of the other active zones are in progress. We emphasize the speed and simplicity of employing brine shrimp as a bioactivity monitor during phytochemical fractionation. (no Refs)

66. SYNTHESIS OF CEPHALOTAXINE ESTERS AND THEIR ANTITUMOR ACTIVITY.

Li S, Sun H, Lu S, Zhang S, Lu F, Dai J, Xu Y

Shanghai Inst. Materia Medica, Academia Sinica, Shanghai, People's Republic of China

Yaoxue Xuebao; 16(11):821-827 1981

Twelve new cephalotaxine esters were synthesized and their antitumor activities studied on three murine experimental tumors (leukemia 615, brain tumor 22 and Ehrlich ascites tumor). Preliminary results showed that the isopropyl (or isopentyl), the tertiary hydroxyl and the methoxycarbonylmethyl groups of their side chain are essential for their antitumor activity. Synthetic procedures are detailed. (6 Refs) (In CHI)

67. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 5'-SUBSTITUTED 5-FLUOROPYRIMIDINE NUCLEOSIDES.

Ajmera S, Danenberg PV
Dept. Biochemistry, Univ. Southern California, Sch. Medicine, Los Angeles, CA, 90033
J Med Chem; 25(8):999-1002 1982

The compound 5'-deoxy-5-fluorouridine (5'-dFUrd, 1) possesses a significantly higher chemotherapeutic index than other fluoropyrimidines as a result of its being selectivity cleaved in tumors to 5-fluorouracil (FUra) by uridine phosphorylase. Because 1 is a relatively poor substrate for this enzyme, we synthesized a series of 5'-deoxy-5'-substituted-5-fluorouridine (FUrd) derivatives in an effort to obtain compounds that might have improved substrate interactions compared to 1 and thus possibly be better prodrugs of FUra. Three derivatives, 5'-O-tosyl-FUrd (13), 5'-O-mesyl-FUrd (14), and 5'-deoxy-5'-bromo-FUrd (15), had cytostatic activity against L1210 and CCRF-CEM leukemic cells in culture superior to that of 1. In preliminary in vivo antitumor studies against L1210 leukemic cells in mice, 5'-deoxy-5'-chloro-FUrd (4), 5'-O-mesyl-FUrd (14), and 5'-deoxy-5'-fluoro-FUrd (18) gave percent increases in life span of 64, 58, and 58, respectively, compared to a value of 20 for compound 1. (Author abstract) (18 Refs)

68. SYNTHESIS AND ANTITUMOR ACTIVITY OF NEW PLATINUM COMPLEXES.

Brown DB, Khokhar AR, Hacker MP, Lokys L, Burchenal JH, Newman RA, McCormack JJ, Frost D
Vermont Regional Cancer Center, Univ. Vermont, Burlington, VT
J Med Chem; 25(8):952-956 1982

A new type of antitumor platinum complex has been prepared and examined for antitumor activity against L1210 leukemia both in vitro and in vivo. The coordination environment of platinum in these complexes consists of three anionic chloride ions and a positively charged amine. The positive charge is introduced by monoprotonation or monoalkylation of a diamine. Platinum(IV) derivatives have been prepared for several of the complexes, and a water-soluble sulfate derivative has been prepared for one of them. Several of these complexes exhibit significant in vitro activity, and trichloro(3-aminoquinuclidinium)platinum(II) (QTP) exhibits significant in vivo activity as well. An increase in life span of approx 40% has been observed using QTP. QTP is toxic at doses slightly in excess of effective doses. (Author abstract) (13 Refs)

69. DIGITIZED VIDEO FLUORESCENCE MICROSCOPY STUDIES OF ADRIAMYCIN INTERACTION WITH SINGLE P388 LEUKEMIC CELLS.

Yanovich S, Taub RN
Div. Medical Oncology, Dept. Medicine, Medical Coll. Virginia, Richmond, VA, 23298
Cancer Res; 42(9):3583-3586 1982

We have evaluated a new fluorescent method, the digitized video fluorescence microscopy technique, for the analysis of Adriamycin drug levels in single-cell suspension. This method uses a Leitz microscope equipped with an HB-50 watt mercury source; the vertical body of the microscope is attached to an intensified silicone intensifier video camera with its output coupled to a video cassette recorder and to an Apple II microcomputer equipped with a video image digitizer. Using this technique, we were able to corroborate previous findings of decreased uptake and increased efflux in resistant as compared to sensitive P388 leukemic cells. This instrument may have wide applications in the study of anthracycline cell interaction or of any other drug with fluorescent properties. (Author abstract) (29 Refs)

70. TERRECYCLIC ACID A, A NEW ANTIBIOTIC FROM ASPERGILLUS TERREUS. 1. TAXONOMY, PRODUCTION, AND CHEMICAL AND BIOLOGICAL PROPERTIES.

Nakagawa M, Hirota A, Sakai H, Isogai A
Dept. Agricultural Chemistry, Univ. Osaka Prefecture, Sakai, Osaka 591, Japan
J Antibiot (Tokyo); 35(7):778-782 1982

A new antibiotic, terrecyclic acid A was isolated from the culture filtrate of a new isolate of fungus, identified as Aspergillus terreus. The fermentation yields reached about one gram per liter of the broth. Chemical and biological characterization of the antibiotic revealed that it was a new sesquiterpene having a wide antimicrobial spectrum and antitumor activity. (Author abstract) (5 Refs)

71. IN VITRO ASSAY OF THE EFFECTS OF PSORALENS PLUS ULTRAVIOLET RADIATION ON HUMAN LYMPHOID CELLS.

Kraemer KH
NIH, Building 37, Room 3E24, Bethesda, MD, 20205
JNCI; 69(1):219-227 1982

An in vitro assay system that mimics some of the features of in vivo oral methoxsalen photochemotherapy (PUVA) in relation to human lymphoid cells was developed. In this assay, suspension cultures of human lymphoid cells were subjected to therapeutic concentrations of 8-MOP and to a UVA radiation spectrum modified to approximate the dermal exposure. The assay permitted correlation and quantitation of multiple 8-MOP plus UVA-induced biological and physical alterations in the same assay system. Thus were demonstrated inhibition of DNA synthesis, reduction of cell survival, production of DNA cross-links, and loss of mixed leukocyte reactivity induced by combinations of 8-MOP and UVA in or near the presumed therapeutic range. This assay may be useful for predicting lymphoid cellular toxicity of other photoactive agents as well as for examining the molecular effects of these agents. (Author abstract) (51 Refs)

INTERFERON AND OTHER ANTIVIRALS

72. EFFECTS OF HUMAN GAMMA INTERFERON ON CELL GROWTH, REPLICATION OF VIRUS AND INDUCTION OF 2'-5'-OLIGOADENYLATE SYNTHETASE IN THREE HUMAN LYMPHOBLASTOID CELL LINES AND K562 CELLS.

Tomita Y, Cantell K, Kuwata T
Dept. Microbiology, Sch. Medicine, Chiba Univ., Chiba 280, Japan
Int J Cancer; 30(2):161-165 1982

Human alpha interferon (IFN-alpha) and beta interferon (IFN-beta) showed antiviral and anticellular effects on human lymphoblastoid Daudi and P3HR-1 cells, but up to 1,000 units/ml of gamma interferon (IFN-gamma) showed no such effect. Though a fairly high level of dsRNA-dependent 2'-5'-oligoadenylate synthetase (2-5A synthetase) was found in Daudi cells, treatment of these cells with IFN-alpha and beta enhanced the enzyme level in cells at least four-fold, but IFN-gamma did not show any such effect. Lymphoblastoid Raji cells were insensitive to the antiviral and anticellular activities of IFN-alpha, beta and gamma, but 2-5A synthetase was induced in cells by the treatment with IFN-alpha and beta, though the enzyme level was lower than that found in interferon-treated Daudi cells. Human leukemic K562 cells were completely insensitive to IFN-alpha, beta and at the same time to IFN-gamma with regard to the antiviral, anticellular activities and to the induction of 2-5A synthetase. (Author abstract) (31 Refs)

73. ISOLATION OF INTERFERON-RESISTANT VARIANTS OF FRIEND ERYTHROLEUKEMIA CELLS: EFFECTS OF INTERFERON AND OUABAIN.

Affabris E, Jemma C, Rossi GB

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Virology; 120(2):441-452 1982

Interferon (IFN)-resistant clones of Friend leukemia cells (FLC) have been isolated by continuous growth in IFN-rich medium followed by plating in semisolid medium in the presence of 1,500 U/ml of IFN. FLC variants are fully resistant to the IFN-induced antiviral state against lytic viruses (Mengo and vesicular stomatitis virus) and retrovirus (Friend-MuLV) production at least up to IFN doses 1,000-fold higher than those needed to protect parental FLC. With respect to erythroid differentiation in dimethylsulfoxide DMSO-induced FLC it is emphasized that: (1) the FLC variant tested was also resistant to the enhancement of erythroid differentiation by low doses (15-480 U/ml) of IFN; (2) IFN doses (5,000-20,000 U/ml) practically unable to reduce Friend-MuLV release and VSV yields did inhibit, instead, the erythroid differentiation of the DMSO-induced FLC variant tested almost at the same extent as with susceptible FLC. The striking dichotomy of IFN-induced antiviral vs differentiation effects suggests that different mechanisms underlie different IFN effects, the specificity of which was fully ascertained by employing pure IFN preparations. In the FLC system, treatment with ouabain does not compete IFN-induced antiviral state. Yet, two out of three variants tested were partially resistant to ouabain-induced inhibition of Friend-MuLV release while being fully susceptible to other ouabain-induced effects on FLC. In addition, an ouabain-resistant FLC variant was not resistant to IFN. (Author abstract) (46 Refs)

74. ACQUISITION OF TOLERANCE TO THE ANTIPROLIFERATIVE ACTIVITY OF INTERFERON BY X-RAY TRANSFORMED C3H/10T1/2 CELLS UNDER PROLONGED TREATMENT WITH INTERFERON.

Brouty-Boye D

Institut de Recherches Scientifiques sur le Cancer, Villejuif, France

Int J Cancer; 30(2):193-195 1982

X-ray-transformed C3H/10T1/2 cells serially passaged in the presence of highly purified mouse interferon appeared to acquire progressively a tolerance to the inhibitory effect of interferon on cell proliferation. In contrast, these cells did not appear to develop a tolerance to the antiviral activity of interferon. These results suggest the possibility that these two effects of interferon are mediated by different mechanisms. (Author abstract) (12 Refs)

75. EFFECT OF CYCLIC AMP AND CYCLIC GMP ON THE ACTIVITY OF INTERFERON AGAINST HERPES SIMPLEX VIRUS TYPES 1 AND 2, AND VESICULAR STOMATITIS VIRUS.

Stanwick TL, Nahmias AJ

Microbiology Dept., Univ. Health Sciences, Chicago Medical Sch., 3333 Green Bay Road, North Chicago, IL, 60064

Arch Virol; 72(4):247-256 1982

The antiviral action of interferon (IFN) on herpes simplex virus (HSV) Types 1 and 2, and vesicular stomatitis virus (VSV) was examined with respect to the intracellular levels of cyclic adenosine monophosphate (CAMP) and cyclic guanosine monophosphate (CGMP) in human fibroblast (HF) cultures. Interferon by itself increased the intracellular levels of CAMP, but had no effect on the CGMP levels. Inoculation of HF with HSV or VSV, however, decreased the CAMP levels. Also, HSV inoculation elevated the CGMP levels, but VSV did not alter the CGMP levels. When HSV and IFN were added to the HF cultures in various combinations, HSV inhibited the IFN-induced elevation of CAMP and increased the CGMP levels to that characteristically observed with HSV inoculation in the absence of IFN. In contrast, IFN antagonized the VSV-associated decrease in CAMP levels. Although the yields of VSV were unaltered by the presence of CAMP- or CGMP-enhancing compounds, the yields of HSV were decreased with CAMP enhancers and increased with CGMP enhancers. The combination of IFN and CAMP enhancers had an additive effect in reducing the yields of HSV. Neither the CAMP or CGMP enhancers affected the action of IFN on VSV. These studies suggest that the interactions observed between HSV and cyclic nucleotides might account for the relatively refractive nature of HSV, as compared to VSV, toward the antiviral activity of IFN. (Author abstract) (23 Refs)

76. INHIBITOR OF SWINE LEUKOCYTIC INTERFERON.

Parfenov VV, Timofeev IV, Zubanova NA

N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR

Vopr Virusol; (3):338-341 1982

The results of evaluation of the properties of inhibitor isolated from the swine leukocytic interferon (SLI) are reported. The inhibitor showed a heterospecific activity against SLI, human leukocytic interferon, and mouse serum interferon. The inhibitor had a marked antiproliferative effect in the culture of normal human fibroblasts and in the culture of ovarian carcinoma and HeLa cells. (23 Refs) (In RUS)

77. NATURAL KILLER CELLS IN RESISTANCE TO VIRUS-INFECTED CELLS.

Rager-Zisman B, Bloom BR

Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY, 10461

Springer Semin Immunopathol; 4(4):397-414 1982

The role of natural killer (NK) cells in resistance to virus-infected cells is reviewed. The following subject areas are covered: NK cells against virus-infected targets, induction of NK activity, characterization of NK cells, recognition of target cells, lytic mechanism, induction of resistance of target cells to interferon-induced NK lysis, the role of NK cells in vivo, and the relevance of NK cells to human disease. It is premature to evaluate the importance of NK cells in human cancer. (117 Refs)

78. SPONTANEOUS PRODUCTION OF ALPHA- AND BETA-INTERFERON IN HUMAN LYMPHOBLASTOID AND LYMPHOMA CELL LINES.

Adolf GR, Haas OA, Fischer P, Swetly P
Wrnst-Boehringer-Institut fur Arzneimittelforschung, Dr.-Boehringer-Gasse 5-11, A-1121 Wien, Austria
Arch Virol; 72(3):169-178 1982

A large number of human hematopoietic cell lines was examined for spontaneous production of interferon. Unconcentrated culture supernatants from 70 out of 71 B-lymphoblastoid cell lines contained considerable amounts of interferon (median titer 22 units per ml); a few lines produced more than 100 units/ml with peak values up to 500 units/ml. In contrast, only one B-lymphoma line out of 18 genuine lymphoma, myeloma, and leukemia cell lines tested spontaneously produced small amounts of interferon. Following treatment with 5-bromodeoxyuridine (BrdUrd), interferon was produced without further induction in most B-lymphoid cell lines, but not in any of the non-B, non-T, T-lymphoid or myeloid lines examined. Modulation of spontaneous interferon production by chemicals (sodium butyrate, dexamethasone, dimethylsulfoxide, a phorbol ester, and BrdUrd) was studied in more detail in three B-lymphoblastoid and four B-lymphoma cell lines. The patterns of responses observed were different for the action of different chemicals on a given cell line as well as between lymphoblastoid and lymphoma lines in general; furthermore, several lines of evidence suggest that chemicals can differentially influence spontaneous and virus-induced interferon production in a given cell line. The composition of spontaneously produced interferon was analyzed using antisera specific for HuIFN-alpha and HuIFN-beta. Interferons produced by untreated as well as BrdUrd-treated lymphoblastoid cells contained more than 95% IFN-alpha, whereas BrdUrd-treated lymphoma cells produced IFN-alpha as well as minor amounts (cell lines Namalwa and NC-37) or even over 90% of IFN-beta (Daudi). (Author abstract) (17 Refs)

79. THE ROLE OF LIVER IN THE CATABOLISM OF HUMAN ALPHA- AND BETA-INTERFERON.

Bocci V, Pacini A, Bandinelli L, Pessina GP, Muscettola M, Paulesu L
Istituto di Fisiologia Generale Universita, 53100 Siena, Italy
J Gen Virol; 60(part2):397-400 1982

The susceptibility of human leukocyte alpha interferon, fibroblast beta interferon and recombinant alpha-2-interferon to clearance by the isolated and perfused rabbit liver has been evaluated. Human leukocyte and recombinant alpha-2-interferons were stable and their initial levels were maintained in the perfusate even if they had been treated with neuraminidase, thus suggesting that alpha-interferons have no exposed sugars recognizable by hepatic binding proteins. On the other hand, native, and particularly desialylated human beta-interferon, underwent marked hepatic uptake confirming the importance of the liver as a catabolic site for glycosylated interferons. (Author abstract) (21 Refs)

80. GENETIC MECHANISMS OF RESISTANCE OF ACYCLOVIR IN HERPES SIMPLEX VIRUS.

Crumpacker CS, Schnipper LE, Chartrand P, Knopf KW
Div. Infectious Disease, Beth Israel Hosp., Room L201, 330 Brookline Ave., Boston, MA, 02215
Am J Med; 73(1A):361-368 1982

Resistance to acyclovir in herpes simplex virus (HSV) is mediated by two genetic loci on the herpes virus genome: viral thymidine kinase and DNA polymerase. Passage of HSV in the presence of 10 uM or 2 uM acyclovir readily coselects for virus deficient in the expression of viral thymidine kinase and resistance to acyclovir. Other workers have shown that passage of HSV in serum-starved cells in the presence of acyclovir selects for a mutant virus possessing a thymidine kinase with an altered substrate specificity and inability to phosphorylate acyclovir. Mutants with temperature-sensitive lesions in the viral DNA polymerase loci of HSV also exhibit resistance to antiviral drug phosphonoacetic acid (PAA) and acyclovir. The mutations conferring resistance to PAA and acyclovir are closely linked within the DNA polymerase locus. The map limits containing mutations that confer resistance to PAA and acyclovir are found within a 1.3 kilobase pair (kbp) region of DNA sequences in HSV-2 (map unit 40.2 to 41.0) and within a 2.6 kbp region of DNA sequence in HSV-1 (map units 40.2 to 41.8). The DNA polymerase loci of HSV also contains a region of DNA sequences to the left of the region defining the resistance mutation which determines the type specific sensitivity of HSV-1 and HSV-2 to acyclovir. Two HSV-1/HSV-2 recombinants were selected for further analysis of resistance. Viral DNA polymerase enzymes were purified from the R6-26 and R6-34 recombinants; the resistant recombinant R6-34 was shown to process an altered viral DNA polymerase. This altered viral DNA polymerase exhibited resistance to three inhibitors of DNA polymerase activity, PAA, acyclovir-TP, and 2'3'dideoxynucleotide triphosphate (didNTPs). The polymerase from R6-34 and the resistant parent possess a much higher Ki for the PAA and the didNTP than do the sensitive strains. A 1.3 kbp region of HSV-1 DNA within the DNA polymerase locus contains resistance mutations to three DNA polymerase inhibitors, codes for an amino acid sequence of 42,000 mol wt, and defines an active center of the HSV DNA polymerase enzymes. (Author abstract) (32 Refs)

81. EFFECT OF 9-(2-HYDROXYETHOXYMETHYL)GUANINE ON VIRAL-SPECIFIC POLYPEPTIDE SYNTHESIS IN HUMAN CYTOMEGALOVIRUS-INFECTED CELLS.

Mar EC, Patel PC, Huang ES

Cancer Res. Center, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514

Am J Med; 73(1A):82-85 1982

Plaque-forming assay resulted in a 50% inhibitory dose by 9-(2-hydroxyethoxymethyl)guanine (acyclovir) against Towne strain human cytomegalovirus (HCMV) of approximately 98 umol. At the drug concentration of 200 umol, we did not detect any significant inhibition of viral DNA synthesis by cRNA-DNA hybridization. However, at this drug concentration, the synthesis of at least two viral-specific late polypeptides (150K and 67K) was significantly retarded up to 48 hr after infection, but resumed at 72 hr. These data suggest that acyclovir or its in vivo transformed derivative had a transient effect on viral-specific polypeptide synthesis in HCMV-infected human fibroblasts at a high drug concentration. (Author abstract) (19 Refs)

82. REPLICATION OF EPSTEIN-BARR VIRUS DNA IN LYMPHOBLASTOID CELLS TREATED FOR EXTENDED PERIODS WITH ACYCLOVIR.

Colby BM, Shaw JE, Datta AK, Pagano JS
Cancer Res. Center, Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Am J Med; 73(1A):77-81 1982

An Epstein-Barr virus (EBV)-producing human lymphoblastoid cell line (P3HR-1) was characterized after prolonged exposure to 9-(2-hydroxyethoxymethyl)guanine (acyclovir). P3HR-1 cells grown for 11 mo in the presence of acyclovir had the same number of EBV genomes (approx 15/cell) as did short-term acyclovir-treated cells. After removal of the drug, the number of EBV genome equivalents of long-term acyclovir-treated cultures (15/cell) returned to P3HR-1 control levels (340/cell). Indirect immunofluorescence studies demonstrated reduced percentages of long-term (6 to 12 mo) acyclovir-treated P3HR-1 cells expressing both EBV early antigens (EA) and viral capsid antigens (VCA). This contrasts with short-term acyclovir-treated cultures where EA is expressed at normal levels even though VCA expression is reduced. Restriction fragment patterns of the total EBV DNA from both short- and long-term acyclovir-treated cultures were identical with the exception of two fragments present in short- but not long-term acyclovir-treated cultures. EBV-associated DNA polymerase was present in long-term acyclovir-treated cultures with the level of activity, as determined by assay in vitro, comparable to that in untreated P3HR-1 cells. The polymerase activity in the treated cells was sensitive in vitro to acyclovir triphosphate, N-ethylmaleimide (NEM), and phosphonoacetic acid (PAA). These studies demonstrate that acyclovir inhibits the EBV-productive cycle in P3HR-1 cells continuously during extended periods of treatment. (Author abstract) (21 Refs)

83. EFFECT OF ACYCLOVIR ON HERPES SIMPLEX VIRUS REPLICATION IN A PERSISTENTLY INFECTED HUMAN LYMPHOBLASTOID CELL LINE (P3HR-1).

Shaw JE, Colby BM, Leong J, Bolling TJ
Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Am J Med; 73(1A):72-76 1982

We examined the effect of acyclovir on herpes simplex virus (HSV) replication in the persistently infected human lymphoblastoid cell line, P3HR-1. During 10 days of continuous exposure of P3HR-1 cells to 100 uM acyclovir there was a decrease in the number of cells expressing HSV antigens, the number of copies of HSV DNA per cell, and the infectivity of extracellular virus. A significant increase in each of these was detected after 14 days of continuous exposure of P3HR-1 cells to the drug, demonstrating that the replication of HSV has become resistant to inhibition by acyclovir. No apparent resistance of EBV replication to inhibition by acyclovir, however, was detected in HSV-infected P3HR-1 cells. The number of copies per cell of EBV and HSV DNA increased after exposure of HSV-infected P3HR-1 cells to the tumor promoter TPA (12-O-tetradecanoyl-phorbol-13-acetate). When cells were exposed continuously to acyclovir for 4 mo and then exposed to acyclovir and TPA simultaneously, the number of copies per cell of HSV DNA increased, but the number of copies per cell of EBV DNA increased by only a few, if any. The detection of P3HR-1 cultures of individual cells expressing both HSV and EBV antigens suggested that HSV and EBV productive cycles could occur simultaneously within the same cell. However, single cells very rarely expressed both antigens simultaneously. (Author abstract) (19 Refs)

84. ACYCLOVIR INHIBITION OF VIRAL DNA CHAIN ELONGATION IN HERPES SIMPLEX VIRUS-INFECTED CELLS.

McGuirt PV, Furman PA
Dept. Experimental Therapy, Wellcome Res. Lab., Research Triangle Park, NC, 27709
Am J Med; 73(1A):67-71 1982

The effect of acyclovir on DNA synthesized in HSV-1-infected cells was examined. Viral DNA synthesis was significantly reduced in the presence of 10 uM acyclovir monitored by cRNA-DNA hybridization and isopycnic centrifugation in cesium chloride. DNA synthesized in infected cells in the presence of acyclovir appeared to be chain-terminated when evaluated by rate zonal centrifugation in alkaline sucrose. Cellular DNA synthesis in actively replicating uninfected cells in the presence of acyclovir was evaluated by isopycnic centrifugation. Cellular DNA synthesis appeared unaffected at concentrations of acyclovir up to 100 uM. (Author abstract) (7 Refs)

85. DIFFERENT IN VITRO EFFECTS OF DUAL COMBINATIONS OF ANTI-HERPES SIMPLEX VIRUS COMPOUNDS.

Schinazi RF, Nahmias AJ
Dept. Pediatrics, Div. Infectious Diseases, Allergy and Immunology, Emory Univ. Sch. Medicine, 69 Butler St., S.E., Atlanta, GA, 30335
Am J Med; 73(1A):40-48 1982

Five promising antivirals have been tested individually and in pairs on herpes simplex virus (HSV) Types 1 (Strain F) and 2 (Strain G) in Vero cells. These are: 9-(2-hydroxyethoxymethyl)guanine (acyclovir, ACV), 9-beta-D-arabinofuranosyladenine (ara-A), 5-trifluorothymidine (TFT), E-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), and phosphonoformate (PFA). Various types of interactions depending on virus type were observed: synergistic [ara-A/TFT; ara-A/BVDU (G); BVDU/PFA (F)]; additive [ACV/ara-A; ACV/TFT; ACV/BVDU; ACV/PFA (G); BVDU/TFT; PFA/ara-A; PFA/TFT]; and sub-additive [ACV/PFA (F); ara-A/BVDU (F) and BVDU/PFA (G)]. Neither antagonism nor interference was noted for any combinations. (Author abstract) (35 Refs)

86. PERSPECTIVES ON INTERACTIONS OF ACYCLOVIR WITH EPSTEIN-BARR AND OTHER HERPES VIRUSES.

Pagano JS, Datta AK
Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Am J Med; 73(1A):18-26 1982

Acyclovir [9-(2-hydroxyethoxymethyl)guanine] inhibits Epstein-Barr virus (EBV) replication in lymphoblastoid cells at concentrations nontoxic to cellular growth. The mode of action of the drug against EBV differs from the mechanism described in herpes simplex virus systems. Due to the absence of virus-specified thymidine kinase, the drug is poorly phosphorylated in EBV-infected cells. The extent of monophosphorylation is similar both in mock-infected and EBV-infected cells. Despite weak phosphorylation of the drug, the replication of linear EBV DNA is inhibited due to exquisite sensitivity of the viral DNA polymerase. Activation of acyclovir does not require phosphorylation by virus-specified thymidine kinase. Inhibition of different herpes-group viruses depends on three variable factors: degree of phosphorylation, cellular metabolism of the drug, and degree of sensitivity of the viral polymerase. Interaction of acyclovir-triphosphate with EBV DNA polymerase is reversible. Cells infected with EBV and treated with acyclovir resume virus replication following removal of the drug even after long exposure. Acyclovir inhibits replication of linear genomes and stops production of virus, but has no effect on latent cellular infection. These results lead us to predict that acyclovir will suppress, but not cure, EBV infection. (Author abstract) (33 Refs)

87. EFFECT OF ACYCLOVIR ON THE DEOXYRIBONUCLEOSIDE TRIPHOSPHATE POOL LEVELS IN VERO CELLS INFECTED WITH HERPES SIMPLEX VIRUS TYPE 1.

Furman PA, Lambe CU, Nelson DJ
Dept. Experimental Therapy, Wellcome Res. Lab., Research Triangle Park, NC, 27709
Am J Med; 73(1A):14-17 1982

The effect of acyclovir on the deoxyribonucleoside triphosphate pools of Vero cells infected with herpes simplex virus Type 1 was examined. Deoxyguanosine triphosphate and deoxyadenosine triphosphate pool levels in infected cells treated with acyclovir increased dramatically compared with pool levels in untreated infected cells. The increases were due, a least in part, to inhibition of viral DNA polymerase activity which resulted in reduced utilization of the deoxyribonucleoside triphosphates. Differences of as much as 26x were detected in the sensitivity of herpes simplex virus Type 1 to inhibition by acyclovir with different Vero cell cultures. These results were due to differences in acyclovir triphosphate levels, not to differences in deoxyguanosine triphosphate levels. (Author abstract) (18 Refs)

88. MECHANISM OF ACTION AND SELECTIVITY OF ACYCLOVIR.

Elion GB
Wellcome Res. Lab., 3030 Cornwallis Road, Research Triangle Park, NC, 27709
Am J Med; 73(1A):7-13 1982

Acyclovir, an acyclic purine nucleoside analog, is a highly potent inhibitor of herpes simplex virus (HSV), Types 1 and 2, and varicella zoster virus, and has extremely low toxicity for the normal host cells. This selectivity is due to the ability of these viruses to code for a viral thymidine kinase capable of phosphorylating acyclovir to a monophosphate; this capability is essentially absent in uninfected cells. The acyclovir monophosphate (acyclo-GMP) is subsequently converted to acyclovir triphosphate (acyclo-GTP) by cellular enzymes. Acyclo-GTP persists in HSV-infected cells for many hr after acyclovir is removed from the medium. The amounts of acyclo-GTP formed in HSV-infected cells are 40 to 100x greater than in uninfected Vero cells. Acyclo-GTP acts as a more potent inhibitor of the viral DNA polymerases than of the cellular polymerases. The DNA polymerases of HSV-1 and HSV-2 also use acyclo-GTP as a substrate and incorporate acyclo-GMP into the DNA primer-template to a much greater extent than do the cellular enzymes. The viral DNA polymerase binds strongly to the acyclo-GMP-terminated template, and is thereby inactivated. (Author abstract) (14 Refs)

89. CHEMOTHERAPY ON HERPES VIRUS, PARTICULARLY THE EFFECT OF ANTIVIRAL AMINO ACID ANALOGUES.

Toyoshima S, Fukuma M, Fujita H, Seto Y
Div. Chemotherapy, Pharmaceutical Inst., Sch. Medicine, Keio Univ, Tokyo, Japan
Excerpta Med Int Congr Ser; 571:148-156 1982

The characteristics and antiviral effects of two selected amino acid analogs, N-naphthalenesulfonyl-DL-tryptophan (A-91) and N-ethyloxycarbonylaminomethyl-L-isoleucine (A-145), are presented. A-91 shows activity in various studies with herpes simplex virus (HSV) Type 1 and 2, and vaccinia virus in vitro and in vivo. A-91 and A-145 during a 1 hr absorption period did not affect the formation of plaques by HSV-1 and HSV-2 and did not inactivate viruses directly. The compounds do not induce interferon in mice. Results indicate both compounds inhibit viral multiplication but not at a very early stage. In female mice intravaginally infected with HSV-2, macroautoradiographic studies after iv administration of 14C-A-92 or 14C-A-145 showed high radioactivity in the genital organs with consequent prolongation of life span. Since HSV-2 is indicated as one of the possible causes of cervical cancer, these compounds may act as antitumor agents on cervical cancer. (5 Refs)

90. HERPES VIRUS SPECIFIC ENZYMES: PROPERTIES, PHYSIOLOGICAL ROLES, AND PHARMACOLOGICAL IMPLICATIONS.

Cheng YC, Nakayama K, Derse D, Bastow K, Ruth J, Tan RS, Dutschman G, Caradonna SJ, Grill S
Dept. Pharmacology, Sch. Medicine, Univ. North Carolina, Faculty Lab. Office Building 231-H, Chapel Hill, NC, 27514
Excerpta Med Int Congr Ser; 571:47-56 1982

After infection of cells with various types of herpes virus, a number of new polypeptides are synthesized, a few of which exhibit specific enzyme activity. A number of enzymes (thymidine kinase, DNA polymerase, DNase, ribonucleotide reductase, deoxyuridine triphosphatase, and uracil-DNA-glycosylase) are discussed in relation with their role of being potential targets for selective antiviral compounds. (79 Refs)

91. ANTIPROLIFERATIVE EFFECT OF (2'-5')OLIGOADENYLATE DISTINCT FROM THAT OF INTERFERON IN LYMPHOID CELLS.

Leanderson T, Nordfelth R, Lundgren E
(c/o Lundgren) Lab. for Cell and Tissue Culture Res., Univ. Umea, S-901 87 Umea, Sweden
Biochem Biophys Res Commun; 107(2):511-517 1982

As previously reported, the continuously cycling lymphoma cell line P3HR-1 reacts to interferon (IFN) with growth arrest by a postmitotic accumulation in G0. A study is presented which shows that in lymphoid cells the 2'-5'oligoadenylate system does not appear to take part in this inhibition. Leukocyte IFN induces 2'-5'oligoadenylate synthetase both in PeHR-1 cells and spleen cells. Both cell types are sensitive to the antiprolifertive effects of IFN. When P3HR-1 cells were incubated in the presence of the reaction product of the synthetase, 2'-5'ApAp, rate of cell growth was reduced, and unlike IFN, the cells did not enter a plateau phase. Analysis of cell distribution showed that 2'-5'ApAp increased the number of cells in the S-phase. Appropriate controls including snake venom diesterase digested 2'5'ApAp, showed the effect was specific for the oligonucleotide trimer. No significant effect was seen after the addition of 2'5'ApA or 3'5'ApAp. IFN induced 2'5'oligo (A) synthetase in P3HR-1 cells. While IFN and 2'5'ApAp inhibited thymidine incorporation in concanavalin A-activated murine spleen cells, IFN caused a G0/G1 increase and 2'5'ApApA increased the S-phase cell number. Thus, the effect of IFN in P3HR-1 cells was not mediated by 2'5'oligo (A). (20 Refs)

92. INTERFERON ENHANCES GUANYLATE CYCLASE ACTIVITY IN HUMAN LYMPHOMA CELLS.

Rochette-Egly C, Tovey MG
Unite INSERM 61, Avenue Moliere, 67200 Strasbourg, France
Biochem Biophys Res Commun; 107(1):150-156 1982

Treatment of the human Burkitt lymphoma derived cell line Daudi with electrophoretically pure human interferon alpha (IFA), which causes a rapid increase in the intracellular concentration of cyclic guanosine monophosphate (cGMP), enhances guanylate cyclase activity. The increase in guanylate cyclase activity in IFA-treated cells resembled that induced by 10 milliM sodium azide in in vitro systems. Neither partially purified nor electrophoretically pure IFA had any effect on guanylate cyclase activity in a cell-free system made from Daudi cells, however. These results strongly suggest that activation of guanylate cyclase in IFA-treated cells is mediated via interaction of interferon with its specific cell surface receptor. The increase in cGMP in IFA-treated cells was calcium-dependent and was abrogated by treatment with the cyclo-oxygenase inhibitors aspirin and indomethacin. (17 Refs)

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